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British Heart Journal

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Congenital heart disease—changes in form and function *Jane Somerville* 1

Haemostatic defects in cyanotic congenital heart disease *P. Henriksson, Gunilla Värendh, and N.-R. Lundström* 23

Location and vascular supply of sinus node in human heart *K. R. Anderson, S. Yen Ho, and R. H. Anderson* 28

Postoperative haemodynamics in tetralogy of Fallot. A study of 132 children *J. A. Joransen, R. V. Lucas, Jr., and J. H. Moller* 33

Echocardiographic study of right and left ventricular dimension and left ventricular function in patients with tetralogy of Fallot before and after surgery *I. Oberhänsli and B. Friedli* 40

Echocardiographic features of secondary left ventricular hypertrophy *D. G. Gibson, T. A. Traill, R. J. C. Hall, and D. J. Brown* 54

Analysis of left ventricular behaviour in diastole by means of finite element method *C. A. Vinson, D. G. Gibson, and A. L. Yettram* 60

Detection of postinfarction left ventricular aneurysms by first pass radionuclide ventriculography using a multicrystal gamma camera *D. S. Dymond, P. H. Jarritt, K. E. Britton, and R. A. J. Spurrell* 68

Failure of aneurysmectomy to improve left ventricular function *M. Sesto, F. Schwarz, K.-U. Thiedemann, W. Flameng, and M. Schlepper* 79

Electrophysiological effects of L 9394 (benzoylindolizine) in man *A. Waleffe, A. Bordalo, P. Bruninx, H. J. J. Wellens, and H. E. Kulbertus* 89

Effects of propranolol and metoprolol on haemodynamic and respiratory indices and on perceived exertion during exercise in hypertensive patients *C. L. A. van Herwaarden, R. A. Binkhorst, J. F. M. Fennis, and A. van't Laar* 99

Baroreflex sensitivity in hypertension during beta-adrenergic blockade *R. T. Krediet and A. J. Dunning* 106

Potential value of thallium-201 scintigraphy as a means of selecting patients for the coronary care unit *F. J. Th. Wackers, K. I. Lie, K. L. Liem, Ellinor Busemann Sokole, G. Samson, Jan van der Schoot, and D. Durrer* 111

Case reports

- Echocardiographic findings in prolapsed aortic cusp with vegetation *M. F. Shiu, D. J. Coltart, and M. V. Braimbridge* 118
- An operation for anomalous origin of left coronary artery *D. I. Hamilton, P. K. Ghosh, and R. J. Donnelly* 121
- Prosthetic valve endocarditis resulting from *Nocardia asteroides* *R. H. Falk, Frances R. Dimock, and J. Sharkey* 125

Notices 128

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British Heart Journal

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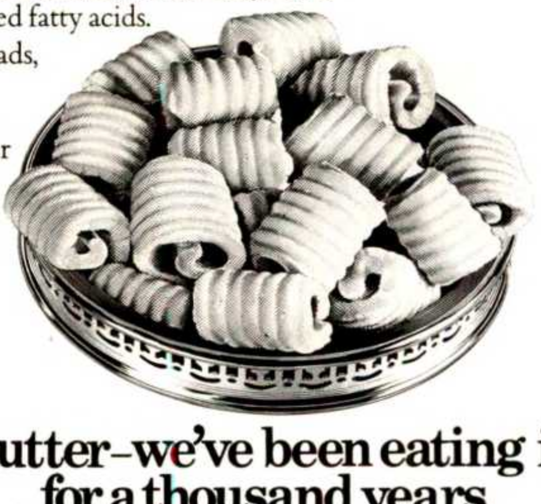

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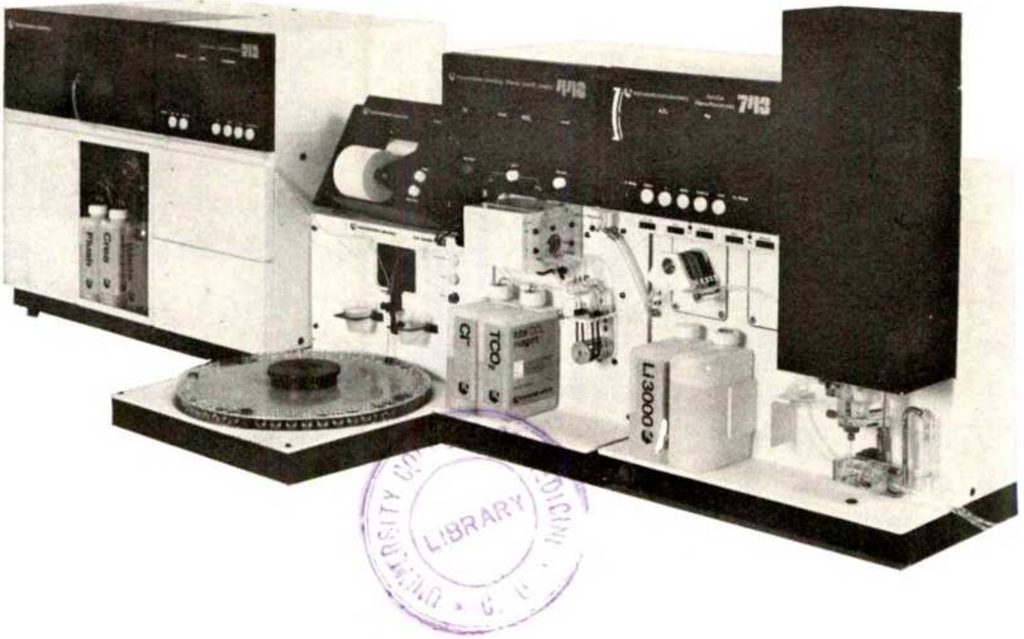

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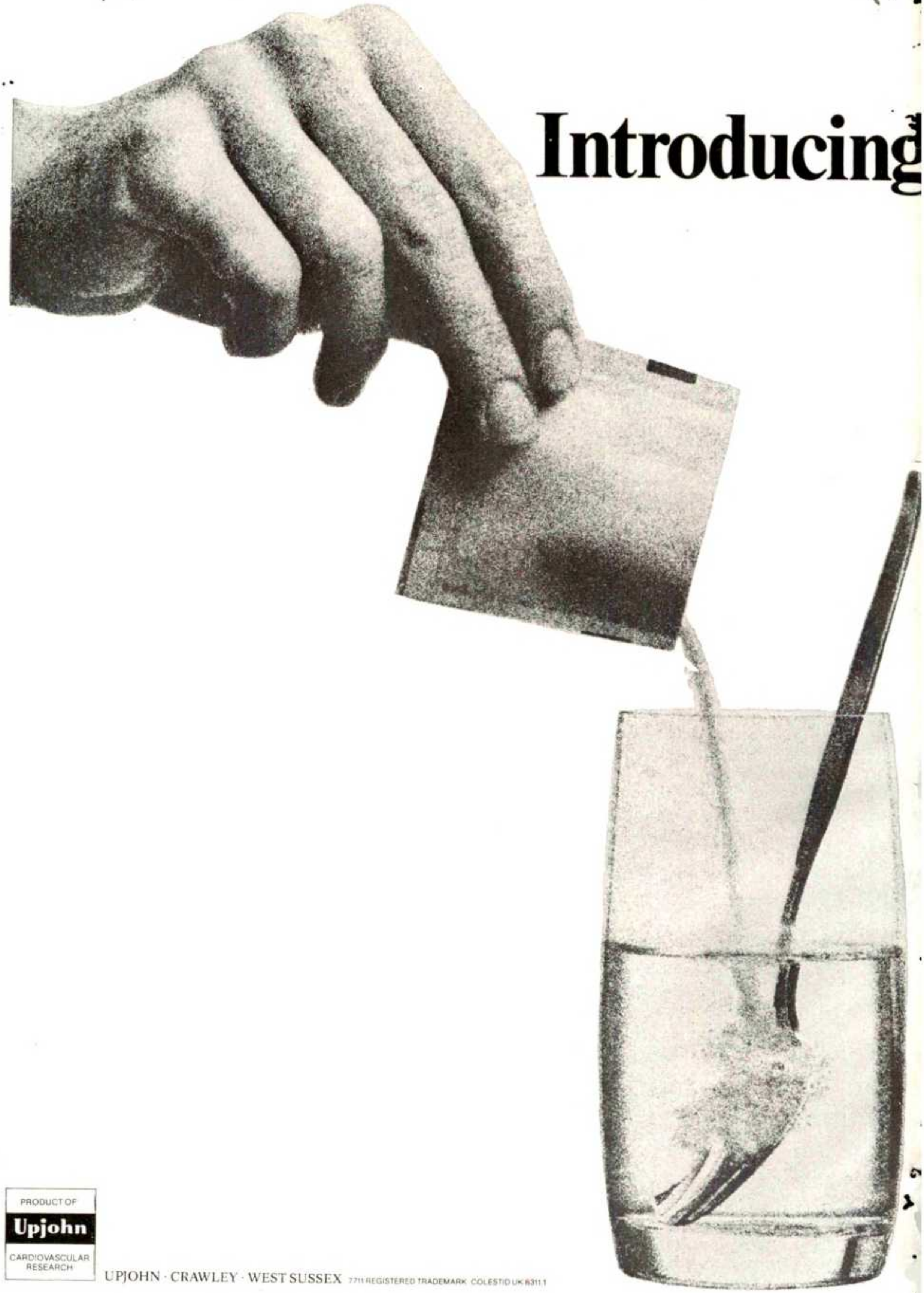

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References: 1. Med J Aust (1973) *1* 1223
2. JAMA (1972) *222* 676
3. New Zealand J Med (1972) *76* 12

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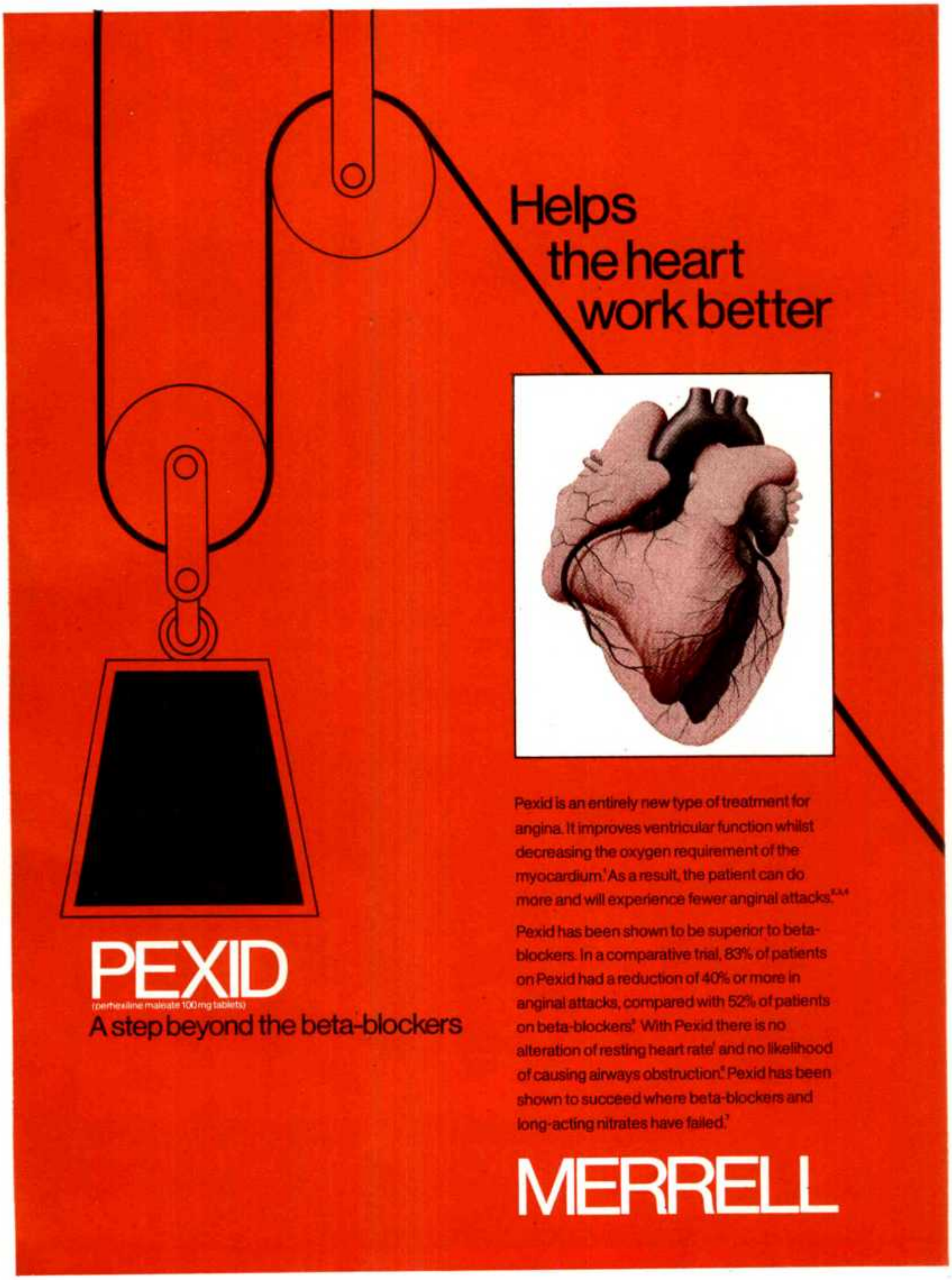
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British Heart Journal, 1979, **41**, 1-22

Congenital heart disease—changes in form and function[1]

JANE SOMERVILLE

From the National Heart Hospital, London

The relation between form and function is the relation between anatomy and physiology; change in one leads to change in the other.

By the time of birth, in babies born alive with cardiac malformations, some adaptive changes in the cardiovascular system already may have been superimposed upon the basic structural abnormalities. These alterations in pathological anatomy continue throughout postnatal life but time is needed for the changes to evolve and show their physiological effects. Such alterations may occur as part of the predetermined natural history and may continue after early palliative surgery has extended the time of survival and thus allowed the abnormal heart to change further its form and function. The interdependence of form and function can be examined in the living from either initial aspect. Congenital heart disease is an ideal model and spontaneous alterations in cardiac form can be detected from changing symptoms, signs, and the use of invasive and noninvasive techniques. With growing experience, many changes are predictable from knowledge of the basic disturbance in cardiac morphology.

In this lecture it is shown how spontaneous change in form influences the natural history of the common anomaly, ventricular septal defect, and the clinical management of patients with this lesion. The various pathological changes which can develop in malformed hearts are then discussed and it is shown how their occurrence influences the signs and symptoms in patients with specific congenital cardiac anomalies, particularly complex malformations.

Ventricular septal defect

Ventricular septal defect (VSD) is the commonest of all congenital cardiac abnormalities (Mitchell *et al.*, 1971). The importance of altered form and function in this condition was recognised by Herbert French, when in 1918 describing a baby with heart failure which later improved he noted that 'the bruits of congenital malformations of the heart may disappear as the child grows up'.

To find out how often this happens, the clinical course of 84 infants in congestive heart failure from large ventricular septal defects was observed for up to 12 years. Initial cardiac catheterisation in 79 showed raised pulmonary artery pressures greater than 50 per cent of the systemic arterial pressure in 76 and large left-to-right shunts at ventricular level in all. Angiography confirmed the presence of an apparently large VSD. None had surgical treatment in infancy for various reasons. The study revealed that there was spontaneous diminution in the size of the VSD in 56 patients and complete closure in 11 (Table). Such changes were documented by phonocardiography (Fig. 1), electrocardiography, chest radiographs, and cardiac catheterisation. As defects became smaller and haemodynamically insignificant the murmur, which was initially pansystolic or long ejection, became early systolic or late systolic before disappearing completely. In some, the late systolic murmur was preceded by a late click (Fig. 1) loudest at the upper left sternal edge and when noted near the apex mimicking the signs of mitral valve prolapse. Indeed, this was often the initial diagnosis when such patients were examined later in life. The late click probably originated from the bulging tricuspid

Table *Fate of 84 infants who presented in heart failure, followed for up to 12 years*

	No.	*Per cent*	
Clinical state same (2 died in first year)	6	7	
Severe increase PVR	5	6	
Became 'Fallot'	6	7	Change in form
Severe inf. stenosis + smaller VSD	2	2	
VSD small	54	65	
VSD closed completely	11	13	
	84		

PVR, pulmonary vascular resistance.

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[1] St Cyres Lecture, 1976.

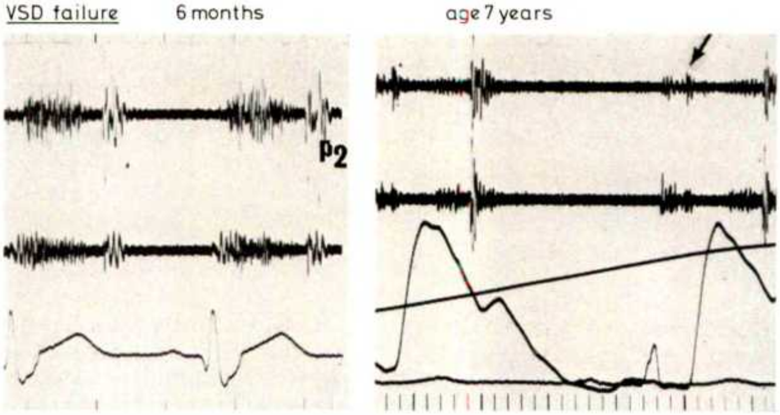

Fig. 1 *Phonocardiograms from a child in failure with large ventricular septal defect (VSD) at 6 months. He improved after 1 year and was a normal child by age 4 years, with signs of a minute VSD. At age 6 months, on the left, there was a long ejection systolic murmur, closely split second sound, and loud pulmonary valve closure (P2). By age 7 years there was only a late systolic murmur at the left sternal edge, a late click (arrow) probably from bulging tricuspid cusp tissue closing the defect, and normal splitting of the second heart sound.*

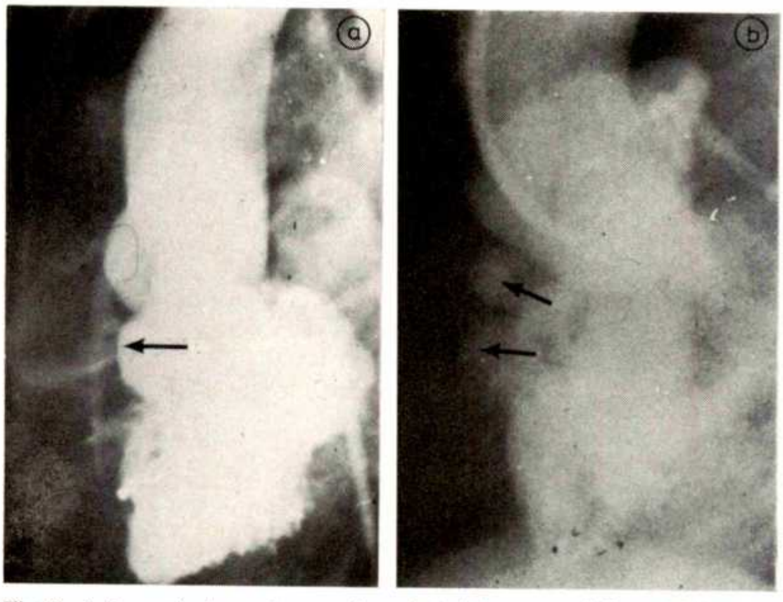

Fig. 2 *Left ventricular angiograms (lateral view) from two children with large ventricular septal defects documented in infancy which had almost closed (a) or completely closed (b). (a) At age 9 years, the tricuspid cusp tissue forms a smooth aneurysmal bulge leaving a small jet where the VSD is still patent (arrow). (b) Age three years. The once large VSD has closed leaving an irregular appearance caused by cusp and fibrous tissue, in the cephalad portion of the ventricular septum beneath the aortic valve (arrows).*

tissue which formed the acquired 'aneurysm' of the membranous ventricular septum seen on the lateral or left anterior oblique views of the left ventricular angiogram (Fig. 2a). Sometimes around the closed or minute defect was an irregular cauliflower like appearance from folds of tricuspid cusp tissue (Fig. 2b). In 5 patients whose defects closed or became very small, disproportionate enlargement and hypertrophy of the left ventricle persisted without any structural lesion to account for it. It is believed that these patients may also have congenital myocardial disease together with a VSD and as such are simple examples of 'diffuse cardiovascular disease' with the VSD being only one part of the congenital problem (Somerville and Becú, 1977). Whether the muscular abnormality progresses or causes symptoms in later life is another problem.

From the Table it is seen that 87 per cent of patients with large ventricular septal defect can change their clinical state as the result of spontaneous alteration of form. Since so many defects become small it is important to know which type of ventricular septal defect is associated with such clinical improvement and to see if this can be recognised at the time the child is ill.

Pathological evidence about spontaneously closed defects is difficult to come by because when improvement in a clinical state occurs, the patient does not usually die. I have seen 2 patients who died after later surgery for associated mitral regurgitation but in whom a large ventricular septal defect, which had been documented earlier, had spontaneously closed. The defects in both had been obviously sited posterior[1] (inferior) to the medial muscle of the tricuspid valve (Fig. 3a). The same was found in a larger series of hearts examined in the Pathology Department of the Children's Hospital, Buenos Aires. When the VSD in this site is viewed from the left side of the heart the upper edge (cephalad) of the defect can be seen to be separated from the aortic valve cusps above by a bar of muscular tissue (Fig. 3b). This is identified on left ventricular angiography by a narrow radiolucency between the under surface of the valve cusps and the contrast media streaming across the upper edge of this type of defect (Fig. 4). There are features on right ventricular angiography which help identify

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[1] The description of cardiac structures depends on how the heart is viewed and by whom—surgeon, pathologist, embryologist, radiologist, or clinician. What is posterior to one is anterior to another and superior to one may be inferior to another. The ventricular septum lies in more than one plane which creates further difficulty in localisation and terminology. In the diagrams, I have tried to make my own terminology clear as seen from inside the right ventricle by a physician looking through the eyes of a surgeon!

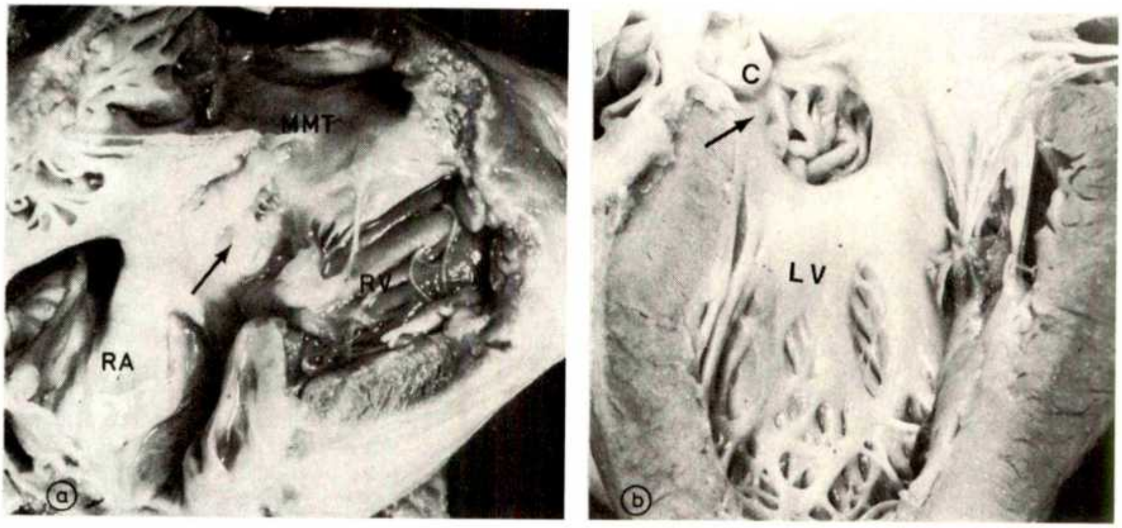

Fig. 3 *Necropsy specimens of heart from patients aged 6 years (a) and 15 years (b) in whom large VSDs have closed. Both had thriving difficulties and failure requiring digitalis in infancy. RA, right atrium; RV, right ventricle. (a) The heart is viewed from the right ventricular side. An arrow marks the site of the 'aneurysm' of the membranous septum formed by cusp tissue of the tricuspid valve which has closed the large VSD sited posterior (inferior) to the medial muscle of the tricuspid (MMT) valve (arrow) also known as the muscle of Lancisi or papillary muscle of the conus. (b) Heart viewed from the left side. Crenations of the cusp tissue can be seen closing the large defect in the ventricular septum. The VSD is separated from the aortic valve cusps (C) by a bar of tissue (arrow). LV, left ventricle.*

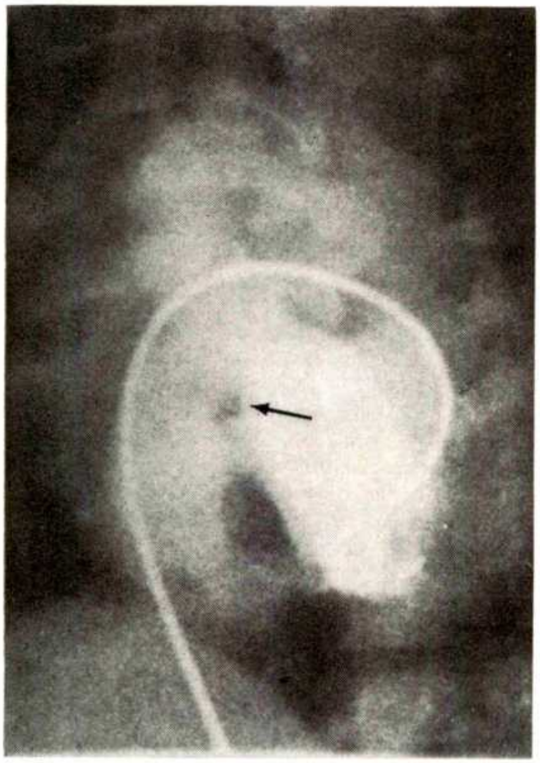

Fig. 4 *Left ventricular cineangiocardiogram (left anterior oblique) from a 9-month-old child with a VSD proven to be posterior (inferior) to the medial muscle of the tricuspid valve by inspection at operation 2 years later when it was found to be closing. The jet of contrast passes from the left across the VSD in the cephalad part of the ventricular septum but the upper edge of the VSD is separated by an area of radiolucency from the aortic valve (arrow). This corresponds to the bar of tissue shown (Fig. 3b).*

this defect by showing the intact convex fossette above the tricuspid valve; this investigation is not usually done in left-to-right shunting ventricular septal defects and so the value of the sign cannot be assessed here.

Many such posterior defects do not close completely but remain surrounded by fibrous and cusp tissue (Fig. 5a) which gives rise to irregularity on the left ventricular angiogram (Fig. 5b) and may be associated with a left ventricle to right atrial shunt. Though these defects do close sometimes in adolescence or adult life they are the ones which are prone to bacterial endocarditis. When associated with a significant shunt and cardiomegaly surgical closure is justifiable particularly if there has been an episode of endocarditis. Hence the reason to identify the anatomy of clinically small or moderate sized VSDs in the 'healthy' child, adolescent, or young adult.

Further evidence about the type of VSDs which close spontaneously comes from the group of infants who presented in failure in the first 3 months with VSD, duct, and coarctation. In 10 such infants who survived surgery for coarctation and left hospital after the first admission, the documented large VSD closed or became very small in 7 with or without banding of the pulmonary artery. It could be argued that these infants were selected by survival and that the anatomy in them was not representative of the whole group of patients with VSD and coarctation as they may not have included certain forms of VSD with a bad prognosis. Despite this theoretical argument, something can be learnt from them. In order to find out what type of VSD occurred in association with this coarctation syndrome a series of 43 hearts was examined from children aged 1 day to 10 weeks who died from cardiac and other causes before or after surgery. In 34 (79%), the defect was posterior to the medial papillary muscle (Fig. 6)—the same incidence as those of the living who improved spontaneously from closure of the defect. Since this posterior defect is so common in the coarctation syndrome presenting in failure in infants under 3 months and this is the defect which shrinks spontaneously, the wisdom of recommending early closure of the VSD or even banding of the pulmonary artery must be questioned and thus the anatomical definition of the exact site and anatomy of the defect in this group is vital.

There is evidence that other VSDs can also close spontaneously. For example, the small single muscular VSD (Fig. 7) may leave a pit when it closes and the small or moderate sized anterior infundibular subpulmonary (supracristal) defect may be physiologically closed by prolapsing aortic cusp tissue. The VSD anterior to the medial papillary muscle (Fig. 8a) bordered by muscle (marked with a ?) and separated from the aortic valve, may be found at operation and necropsy to be encircled by fibrous tissue; whether it can close completely is uncertain but it is possible from its appearance.

Perhaps more important are the VSDs which cannot close or reduce in size (Fig. 8b). The large posterior inlet septal defect (Fig. 8b (a)) which extends completely to the posterior border of the atrioventricular valve ring beneath the attachment of the whole septal leaflet of the tricuspid valve remains large, causing symptoms. This uncommon defect, sometimes referred to as a 'canal' type VSD

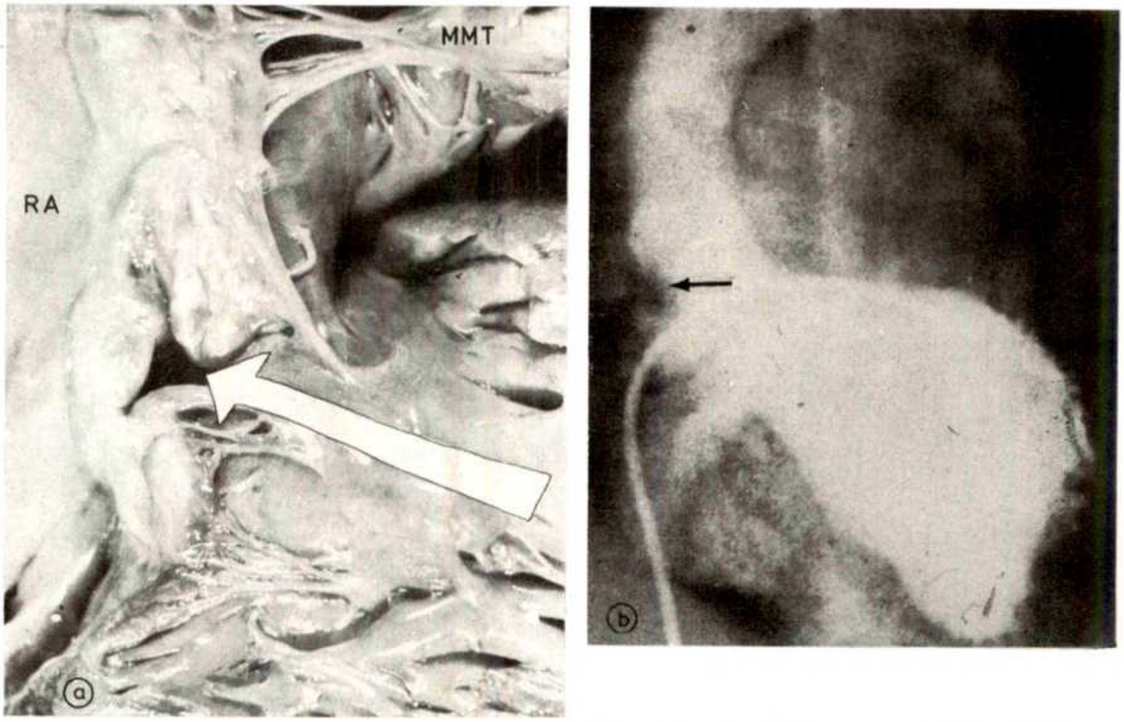

Fig. 5 *(a) Necropsy specimen from a girl aged 14 years viewed from the right ventricle showing a partially closed VSD (white arrow) posterior to the medial muscle (MMT). The VSD is surrounded by irregular cusp tissue and associated in life with a left ventricle to right atrial shunt. RA, right atrium. (b) Left ventricular angiocardiogram (left anterior oblique view) from a living patient with the same defect as shown in (a). The irregularity in the region of the defect is obvious as is the separation from the aortic valve (arrow).*

(Neufeld *et al.*, 1961), can be identified on the left ventricular angiogram not only by the wide separation of its cephalad edge from the aortic valve but also by the broad irregular jet of contrast medium which spreads through the chordal and cusp tissue into the body of the right ventricle. Patients with this VSD frequently have left anterior hemiblock on the electrocardiogram, but since the atrioventricular septum is not absent as it is in persistent atrioventricular canal from which it should be differentiated, the mitral valve is not displaced apically and does not with the deficient ventricular septum, form the characteristic 'gooseneck' appearance of the left ventricular outflow tract on the anterior-posterior view of the left ventricular angiogram (Baron *et al.*, 1964).

The most frequent large ventricular septal defect which does not close (Fig. 8b (b)) lies anterior (superior) to the medial muscle of the tricuspid valve, immediately beneath the aortic valve cusps which forms its cephalad border (Fig. 9a). The attachment of the septal cusp of the tricuspid valve posterior (or inferior) to this defect has a variable relation to it particularly when the lesion is part of the tetralogy of Fallot where the normally formed medial papillary muscle may be absent and its function is taken over by other identifiable septal muscles. This subaortic defect cannot close with its moving upper border of opening and closing cusps. The recognition of this VSD on angiography is simple because the dye outlines the aortic cusps which form the superior border (Fig. 9b). The defect is large and with the aortic root grows as the heart grows during postnatal life. Indeed, the aortic root has a characteristic shape quite different from the small root associated with other forms of equally large VSDs. The size and shape of the aortic root is mainly related to the type of VSD beneath it rather than the size of the left-to-right shunt.

This type of superior subaortic VSD is commonly associated with congenital anterior displacement of the infundibular septum (Fig. 9a) which leads to pulmonary stenosis. However, the

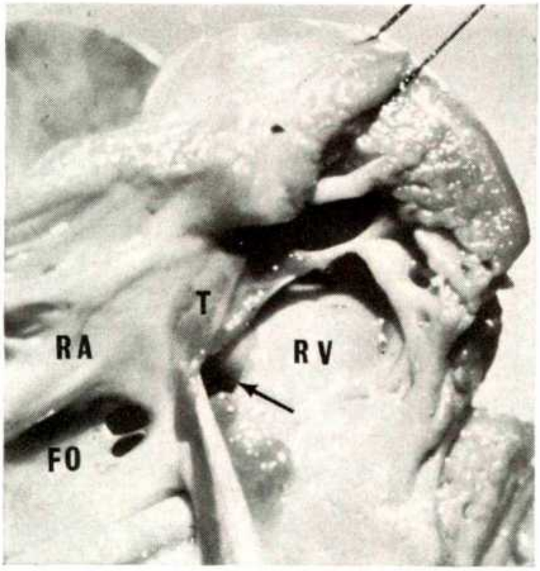

Fig. 6 *Clinically large VSD (arrow) posterior to the medial muscle of the tricuspid valve (T) from a 3-week-old infant and associated with coarctation and duct who died before surgery for the coarctation. There is no evidence of closure because there has not been time. RV, right ventricle; RA, right atrium; FO, fossa ovalis.*

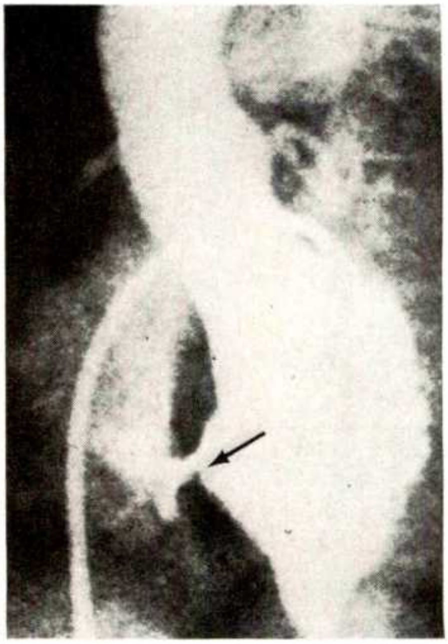

Fig. 7 *Left ventricular angiogram from a child aged 3 years with a small muscular ventricular septal defect which closed by the age of 5 years. The jet passes through the hole 'low' in the septum from the centre of a pit (arrow).*

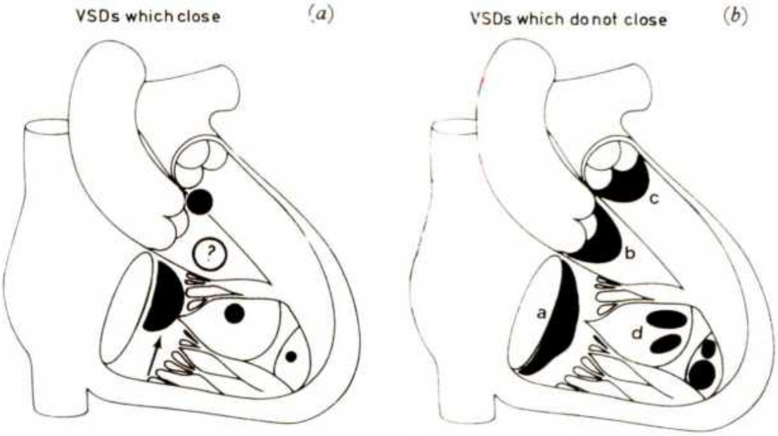

Fig. 8 *(a) Diagram of the heart viewed from the right side to show the site of ventricular septal defects which can close or diminish in size spontaneously. The arrow shows the VSD posterior (or inferior) to the medial muscle of the tricuspid valve, which most frequently behaves in this way. (b) Ventricular septal defects which do not close spontaneously. a: Complete defect which is posterior (inferior) to the medial muscle which extends to the posterior tricuspid ring—so-called inlet VSD or previously referred to as 'canal-type VSD'. b: Subaortic VSD with cephalad border formed by the aortic cusps. c: Large anterior infundibular subpulmonary VSD—may be part of Taussig-Bing complex. d: Multiple muscular VSDs (Swiss cheese).*

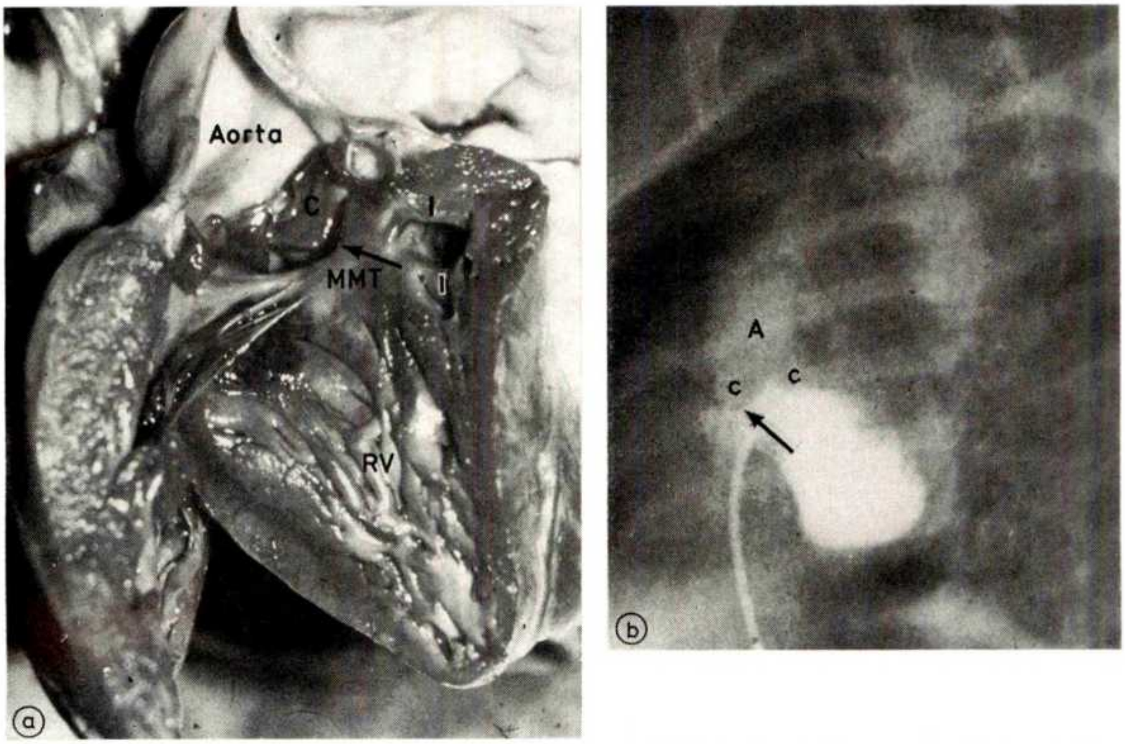

Fig. 9 *Subaortic VSD (8b (b)) which does not close. (a) Heart of a newborn who died in congestive failure, viewed from the right ventricle, the VSD (arrow) is anterior (or superior) to the medial muscle of the tricuspid valve. The aortic cusps (C) are forming the upper part of the defect. The bands of the infundibular septum (I), parietal and septal, are abnormally rotated as in tetralogy of Fallot so that in time an infundibular stenosis will form. (b) Left ventricular angiogram (lateral) from a 1½-year-old child with proven defect of the type illustrated in 9a. The catheter has been passed from the right ventricle through the VSD in the subaortic position into the left ventricle. The contrast medium outlines the aortic cusps forming the roof of the defect (arrow). The aortic root (A) is large and characteristically shaped above this type of VSD. C, aortic valve cusps.*

same defect may be associated with a hypoplastic infundibular septum and no obstruction to the right ventricular outflow either at birth or acquired later. As the defect remains large throughout life, clinical improvement can thus not occur unless pulmonary vascular disease develops. These patients are particularly the ones who develop the Eisenmenger reaction (Wood, 1958) and such was the defect in Eisenmenger's original description (1891). Thus, if this defect is detected without evidence of displaced infundibular septum (or an outflow gradient) it should be closed early. Occasionally the subaortic VSD can become partially obstructed by prolapse of aberrant redundant tricuspid tissue (Scott *et al.*, 1976) and such a complication should be suspected in tetralogy of Fallot if the electrocardiogram shows unusually severe right ventricular hypertrophy and P pulmonale or if the right ventricular pressure exceeds the aortic systolic pressure.

Other types of ventricular septal defect in which there is no evidence of spontaneous closure include the large subpulmonary infundibular defect in the right ventricular outflow tract and the large anterior infundibular defect in which part of the infundibular septum is displaced into the left outflow causing subaortic obstruction often associated with congenital aortic anomalies (Becú complex) (Fig. 8b (c)). Large multiple muscular defects ('Swiss cheese') also do not close (Fig. 8b (d)).

This account of the changes in form and function associated with ventricular septal defect shows how the natural history varies in relation not only to the size of the defect at birth but also to its site and to associated lesions. I believe now that a diagnosis of VSD alone is inadequate for correct management. The site and also size should be specified in order to predict the natural history and recommend surgical treatment at the correct time.

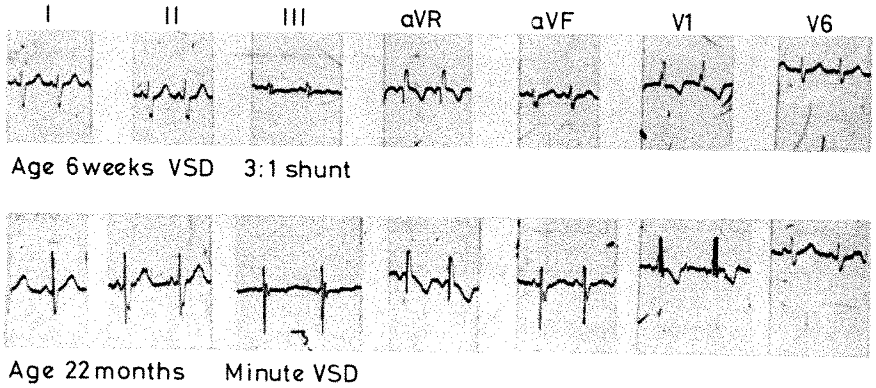

Fig. 10 *Serial electrocardiograms from a child who presented at age 6 weeks with thriving difficulties and mild heart failure. Cardiac catheterisation at age 2 months showed a 3:1 left-to-right shunt and raised pulmonary artery pressure 50/10 mmHg (systemic 60/30 mmHg). By 22 months the heart was normal in size with a short early systolic murmur at the left sternal edge. The upper record shows right axis deviation and probable right ventricular hypertrophy. By age 22 months the electrocardiogram showed left anterior hemiblock and partial right bundle-branch block with normal PR interval.*

UNWANTED SEQUELAE AFTER CLOSURE OF VENTRICULAR SEPTAL DEFECT

Spontaneous closure or reduction in size of a ventricular septal defect usually results in the improvement of the patient but occasionally the pathological process may leave residual effects on the conducting tissue or the tricuspid valve. For example, the electrical axis may become abnormal as the ventricular septal defect closes with eventual development of left anterior hemiblock (Fig. 10). Whether this can progress to complete heart block later is not known but it is theoretically possible.

In adults with small long-standing left ventricular to right atrial shunts due to the septal cusp of the tricuspid valve partly occluding the defect, premature atrial fibrillation from additional pathology such as alcohol or pulmonary emboli, etc may be associated with apparently severe tricuspid regurgitation in middle age, with a small measured shunt which does not account for the severe symptoms. Restoration of the patient to sinus rhythm, if possible, is the best solution.

Before large ventricular septal defects close, serious changes in the peripheral pulmonary arterioles may already have become established. In 2 patients, now aged 6 and 10 years, with angiographically proven closure of once large VSDs the resting pulmonary artery pressures remain at 55/30 mmHg and 45/25 mmHg. Whether this pulmonary hypertension will progress or regress is not known. It is interesting to speculate that these patients may present years later with what might appear to be pulmonary primary or thromboembolic hypertension if the early history is unknown or forgotten. When VSDs close in association with classic transposition of the great arteries serious left ventricular obstruction may result from protrusion of the 'aneurysm' below the pulmonary valve (Fig. 11a and b).

Pathological mechanisms of changing cardiac form

Spontaneous alterations of cardiac anatomy and physiology result from several different pathological mechanisms. Fibrosis from turbulence commonly influences natural history in congenital heart disease in many ways. Another important change is hypertrophy of muscle which not only affects the whole ventricle as a response to increased work demands as in stenotic valves but it may also occur in a more irregular fashion as part of a healing process after earlier infarction or myocardial necrosis. The capacity for this to occur before the age of 5 years is remarkable as can be seen in survivors of infarction associated with anomalous origin of the left coronary artery. More influential in altering the natural history of certain congenital cardiac malformations is 'selective' hypertrophy of congenitally abnormally placed muscular bands which result in acquired obstruction to the egress of blood.

Another pathological change affects atrioventricular valves either secondary to ventricular changes or due to valvular incompetence from abnormal stresses as the result of the disturbed haemo-

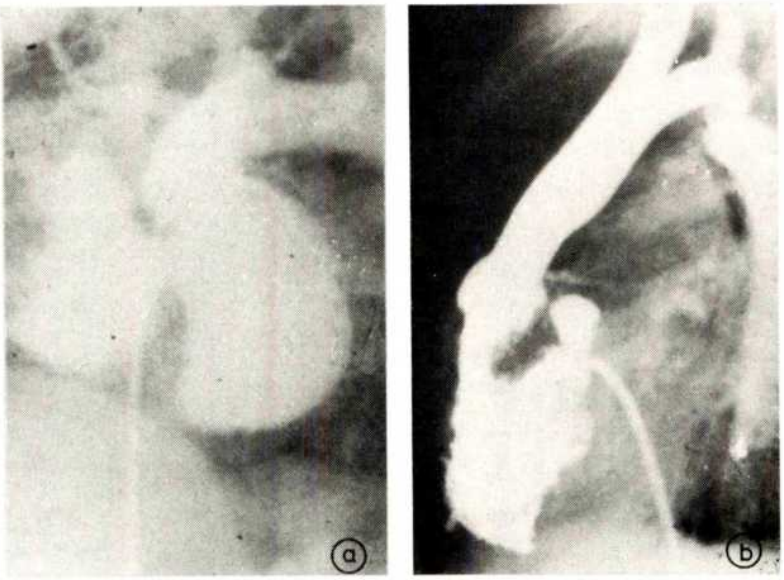

Fig. 11 *Angiograms from a child with classic transposition of the great arteries and ventricular septal defect which closed spontaneously and the 'aneurysm' of the septum protruding into the left ventricular outflow causing serious pulmonary stenosis. (a) Left ventricular angiogram (lateral) showing large VSD and no obstruction between left ventricle and pulmonary valve at age 6 months. (b) Right ventricular angiocardiogram in same patient aged 6 years, showing no evidence of VSD but there is a pouch of tissue protruding into the posterior left outflow causing serious subpulmonary obstruction with a gradient of 85 to 90 mmHg between left ventricle and pulmonary artery. It may be relevant to the morphology that a coarctation was present.*

dynamics from the underlying defect or added anatomical abnormality of the valve and attachments. The addition of mitral or tricuspid regurgitation to an already complicated heart may be disastrous.

The commonest pathological change which occurs with age is calcification. This is most often seen in semilunar valves but also appears in atrioventricular valves, in jet lesions, and myocardial scars.

FIBROSIS STIMULATED BY TURBULENCE

The basic mechanism which closes most VSDs is platelet deposition and fibrosis aided by the sealing curtain effect of the septal cusp of the tricuspid valve. Fibrosis may also develop at other sites in the heart such as in jet lesions on semilunar and atrioventricular valves, on endocardium in the ventricles opposite defects or regurgitant streams, or help late closure of the duct. Fibrosis may disturb vulnerably placed conducting tissue and affect the natural history in certain lesions such as Ebstein's anomaly, corrected transposition, and atrioventricular defects.

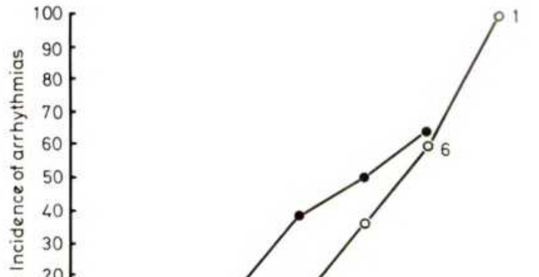

Fig. 12 *Incidence of disorders of rhythm in relation to age of 169 patients with unoperated ostium primum atrial septal defects. Black dots show those who developed spontaneous nodal bradycardia and tachycardia or heart block (including sudden asystole). Open circles show the incidence of paroxysmal and established atrial fibrillation. Nodal rhythms and block occurred occasionally in childhood and adolescence but after age 20 years were common. Atrial fibrillation was common in those who survived beyond 40 years.*

An example of such an effect can be found in the study of ostium primum atrial septal defects, a lesion where survival in the natural course to the fourth or fifth decades is possible (Somerville, 1965). In this lesion the conducting tissue is specially vulnerable because the atrioventricular node lies behind the posterior edge of the defect, and the bundle of His is close to the exposed upper border of the ventricular septum. These areas are subject to chronic turbulence associated with the left ventricular to right atrial and interatrial shunts and so one might expect that disturbances of nodal function and conduction might appear with time. The incidence of spontaneously occurring nodal rhythm disorders and heart block in relation to the age when they appeared in 169 unoperated patients with the ostium primum defect is shown (Fig. 12). As expected, the incidence of such rhythm disorders increased with the age of the patient; fibrosis has been shown in the area of the atrioventricular node as well as in the contiguous conducting bundles. There are other ways in which conducting tissue may be affected in congenital heart disease, and in the conditions where this occurs the conducting tissue may be in an abnormal site and thus more prone to secondary changes.

HYPERTROPHY IN DISPLACED OR DYSPLASTIC MUSCLE BUNDLES

An important and frequent adaptive change is hypertrophy of the myocardium. When this occurs in displaced muscular bands of the infundibular septum it leads to outflow obstruction, at first labile and subsequently fixed as fibrosis occurs. Enlargement of ventricular septal muscle, when dysplastic, can cause outflow obstruction on both sides of the heart asymmetrically or as part of diffuse left ventricular hypertrophy. The factors that influence the development of acquired muscular obstruction in congenital heart disease are the following: abnormally placed muscle bands, the amount of dysplastic muscle present and the stimuli to hypertrophy, high pressures secondary to other lesions, activity of the child, and perhaps additional biochemical factors which may be important after childhood.

Depending on the basic congenital abnormality and the site of the abnormal muscular bands, the

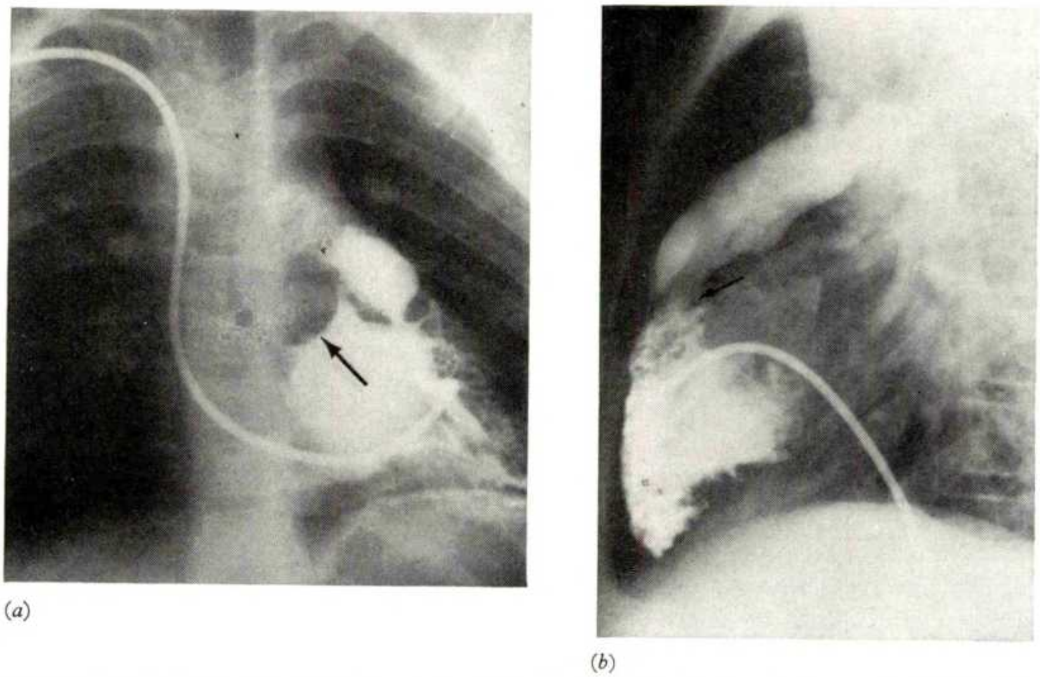
(*a*)

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Fig. 13 *Classic morphology of acquired infundibular obstruction shown on right ventricular angiograms in 2 patients. (a) Anteroposterior view from a 4-year-old child. The under surface of the aortic valve is outlined (arrow) where contrast medium has crossed the subaortic defect. (b) Lateral view showing a clear infundibular stenosis (arrow) composed of fibrous and hypertrophied muscle. The pulmonary valve is normal and the pulmonary arteries are large showing that they have once carried an increased blood flow or have been dilated by a raised pressure.*

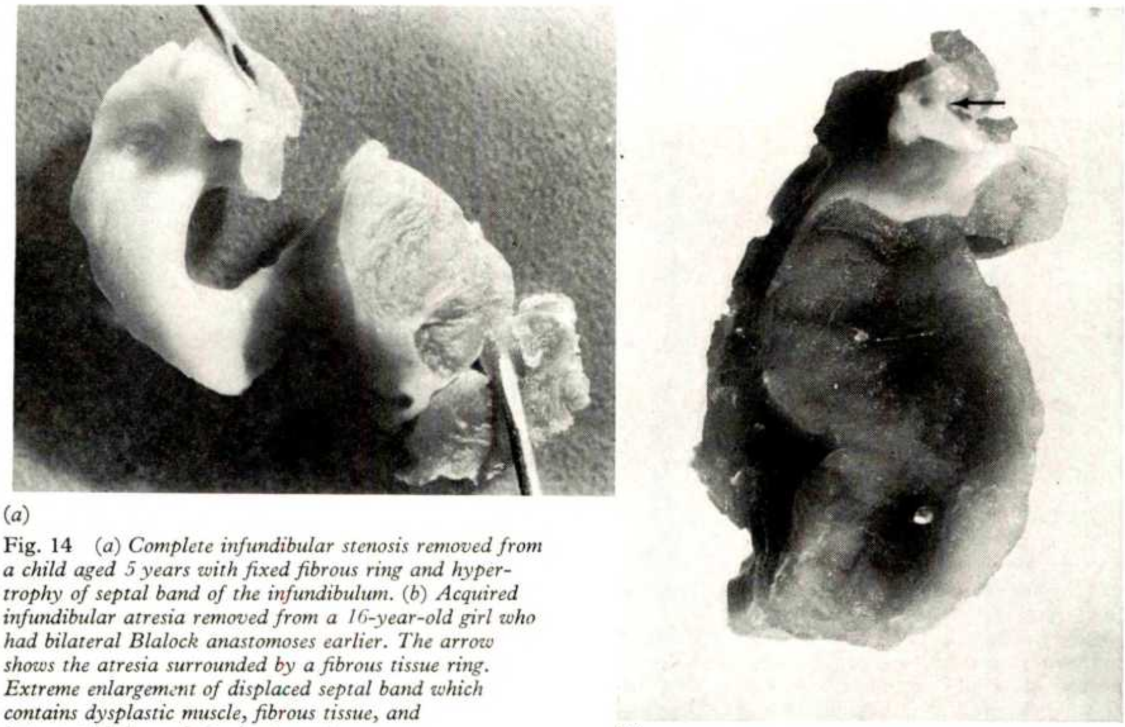
obstructions will affect the cardiac function in different ways.

ACQUIRED OBSTRUCTION IN NORMALLY PLACED RIGHT VENTRICULAR OUTFLOW TRACT (WITHOUT TRANSPOSITION OR MALPOSITION)

In the original series of infants with large ventricular septal defect, it is seen that serious infundibular pulmonary stenosis developed in 8 of the 84 patients who had been in heart failure (Table). Of these, 6 developed the features of tetralogy of Fallot, first with cyanotic attacks and later with chronic cyanosis and effort dyspnoea in their first 2 years, a course described by Becú *et al.* (1961). As the infundibular obstruction in the right ventricular outflow developed, the physical signs changed. On auscultation and phonocardiography, pulmonary valve closure became delayed and diminished and the systolic murmur developed a diamond shape difficult to differentiate with the ear. The electrocardiogram maintained or developed right axis deviation and increasing right ventricular hypertrophy, with diminution of left ventricular voltage in V6. Chest radiographs were slower to change and lagged about 6 months behind in showing progressive reduction in heart size and pulmonary blood flow. The haemodynamics altered appropriately and the infundibular obstruction was confirmed angiographically (Fig. 13a and b).

In 6 of the 8 patients the ventricular septal defect was anterior to the medial muscle of the tricuspid valve and immediately subaortic and thus unable to close (Fig. 9a). In the other 2 patients who acquired severe infundibular obstruction the VSD was posterior to the medial muscle, and at surgery, age 7 years, was small in 1 and closed spontaneously forming a septal aneurysm in the other (Watson *et al.*, 1969).

Haemodynamically important infundibular obstruction can only be acquired under special circumstances. Firstly the infundibular septum (bands of the crista) must be congenitally displaced (Fig. 9a). A stimulus to right ventricular hypertrophy is then probably needed for these to enlarge. Initial obstruction is mild, reducing the pulmonary blood flow. As it increases it may respond to inotropic stimulation and cause cyanotic attacks. Subsequently fibrosis occurs to fix the obstruction and inhibit myocardial growth. The patient may lose the propensity to have cyanotic attacks, to become chronically cyanosed and disabled.



(*a*)

(*b*)

Fig. 14 (*a*) *Complete infundibular stenosis removed from a child aged 5 years with fixed fibrous ring and hypertrophy of septal band of the infundibulum.* (*b*) *Acquired infundibular atresia removed from a 16-year-old girl who had bilateral Blalock anastomoses earlier. The arrow shows the atresia surrounded by a fibrous tissue ring. Extreme enlargement of displaced septal band which contains dysplastic muscle, fibrous tissue, and hypertrophied muscle is also present.*

The pathological form of the infundibular obstruction depends not only on the type of congenital disorder of the infundibulum but also on the age of the patient at operation or death. The older the child, the more the fibrosis and fixed obstruction. In infants below 2 years the muscular bands are hypertrophied and covered by thickened endocardium and later an incomplete or complete ring of fibrous tissue surrounded by muscle is found (Fig. 14a and b). In adolescents and adults huge eccentric masses of infundibular muscle invaded extensively by fibrous tissue as well as thick fibrotic endocardial rings are found. One wonders if the giving of digitalis to the infant in heart failure with this form of infundibular septal rotation hastens the onset of cyanotic attacks. Without the stimulus to hypertrophy from right ventricular hypertension, would the infundibular stenosis develop so severely? Probably not, but it does occur in patients whose VSDs close, but presumably by the time a process has reduced the size of the defect the infundibular obstruction has already become severe enough to increase the right ventricular pressure and perpetuate its own development. In small VSDs associated with aortic regurgitation, the right ventricular pressure is usually not raised from left-to-right shunts as the defects are small. However, this form of abnormal infundibular rotation is commonly present but rarely causes severe obstruction in the first decade, presumably because of the lack of right ventricular hypertension to stimulate secondary hypertrophy.

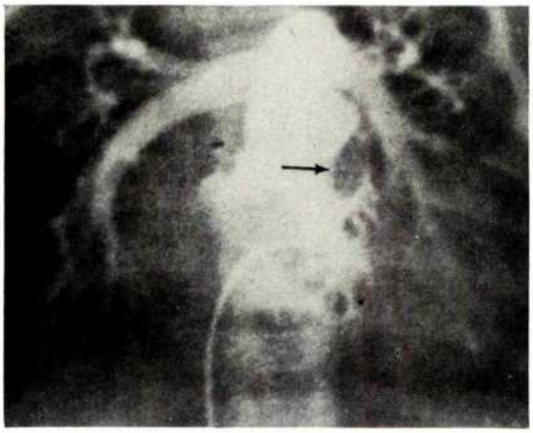


Fig. 15 *Right ventricular angiocardiogram from a week old baby in heart failure with pulmonary artery pressure 10 mmHg below the systemic pressure and a large left-to-right shunt at ventricular level. The child improved with medical treatment and at 13 months developed cyanotic attacks. The displaced abnormal infundibular septum is shown (arrow) and the pulmonary valve is slightly thickened.*

It is important to predict which patients with large ventricular septal defects in heart failure will develop such outflow obstruction so that improvement can be predicted, parents can be warned about cyanotic attacks, digitalis can be stopped early, and the ventricular septal defect can be closed at the right time. Displacement of the infundibular septum can be identified on right ventricular angiocardiography even before significant obstruction occurs, for the displaced bands are obvious in the right ventricular outflow (Fig. 15). In these babies it is worth waiting for spontaneous improvement with medical help and recommending surgery when the infant is larger. In all such patients, however cyanosed, the anatomy is favourable for radical correction as the pulmonary arteries are large. This demonstrates the important concept in congenital heart disease that size reflects use even if it has been in the past.

Infundibular stenosis with Fallot type subaortic VSD can progress to complete atresia (Fig. 14), particularly in patients who develop cyanosis early and who have never been in heart failure but have had a palliative shunt to survive. If they survive to adult life the outflow may even become calcified. Patients with infundibular atresia, however disabled and hypoxic, always have central pulmonary arteries which may stop growing; eventually secondary changes in the lung vessels can prevent a successful outcome of corrective surgery and there may still be a place for a preliminary shunt procedure to redevelop the pulmonary circulation. The infundibular septum may also be abnormally rotated in other conditions such as common atrioventricular canal, double outlet right ventricle, absent pulmonary valves, and common atrium with ventricular septal defect as well as other types of ventricular septal defect already mentioned. Eventually all such patients develop infundibular stenosis and reduction of pulmonary blood flow. This outflow anomaly does not occur with lone secundum atrial septal defect and if a patient is seen in childhood or adolescence with this combination one should assume that a VSD has been present and closed spontaneously.

When subpulmonary stenosis develops with these other lesions, the physiological and clinical effects are the same as with isolated subaortic VSD and the heart becomes smaller. However, when infundibular obstruction develops in patients with common atrioventricular canal and associated double outflow right ventricle, progressive right ventricular dilatation with increasing atrioventricular valve regurgitation appears together with

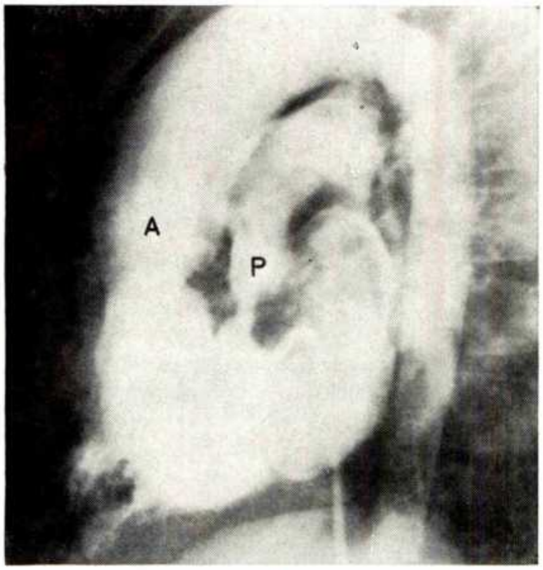


Fig. 16 *Angiogram from a 19-year-old boy with a univentricular heart and anterior aorta (A). A severe subpulmonary obstruction is present beneath a minimally stenosed pulmonary valve and a normal pulmonary artery (P). The infundibular stenosis was lined with radiologically visible calcium.*

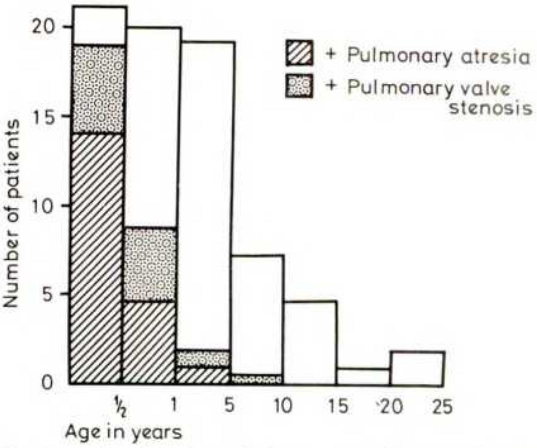


Fig. 17 *Age when hypoxia became a problem needing a palliative shunt in 74 patients with tricuspid atresia and normally related great arteries. Patients with added pulmonary atresia and pulmonary valve stenosis have been shown separately. In the majority, obstruction to pulmonary flow was the result of shrinkage of the VSD.*

cyanotic attacks and widening right bundle-branch block. Another form of acquired right ventricular muscular obstruction occurs when there are anomalously placed muscle bundles 'low' in the outflow at the entrance of the infundibulum. When they hypertrophy a two-chambered right ventricle forms, usually seen after the first decade and with or without VSDs at various sites.

Acquired subpulmonary obstruction in complex lesions

Obstruction which limits the pulmonary blood

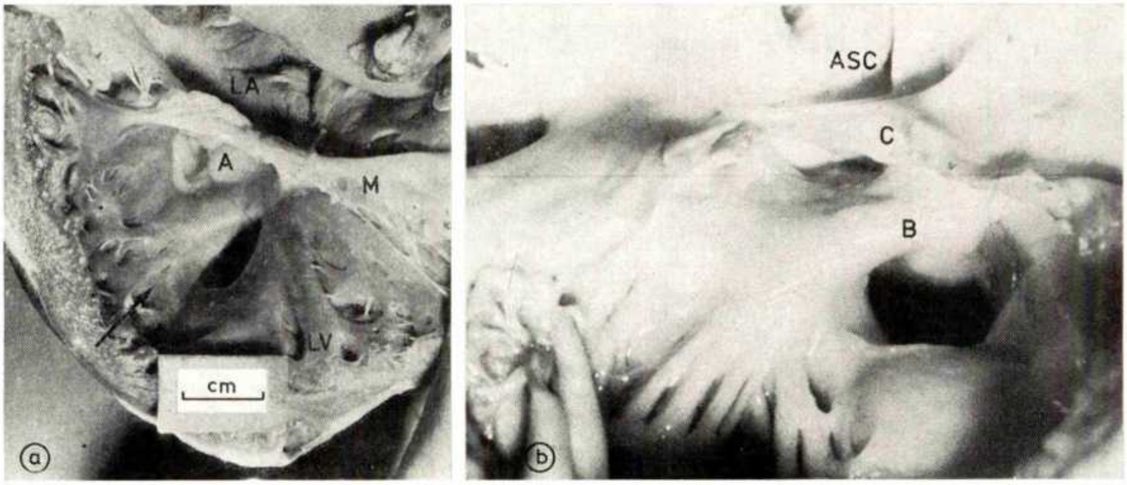
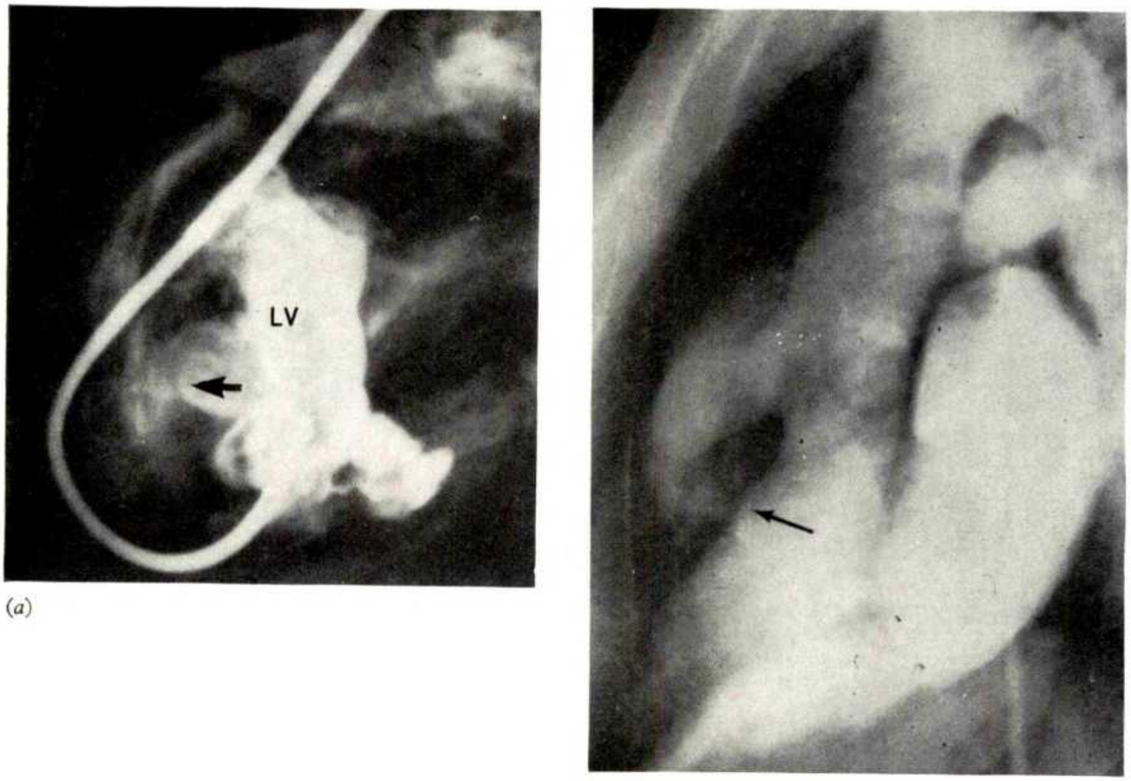


Fig. 18 *Ventricular septal defects in tricuspid atresia in babies dying with heart failure—viewed from the left ventricle. (a) Linear type of VSD (arrows) in the muscular septum which diminishes in size early usually. M, mitral cusp; A, aortic valve cusps; LA, left atrium. (b) Large window type of VSD beneath the aortic valve (C) and separated from it by a bar of muscular tissue (B). ASC, ascending aorta. This defect, when large, takes a longer time to close or reduce in size.*



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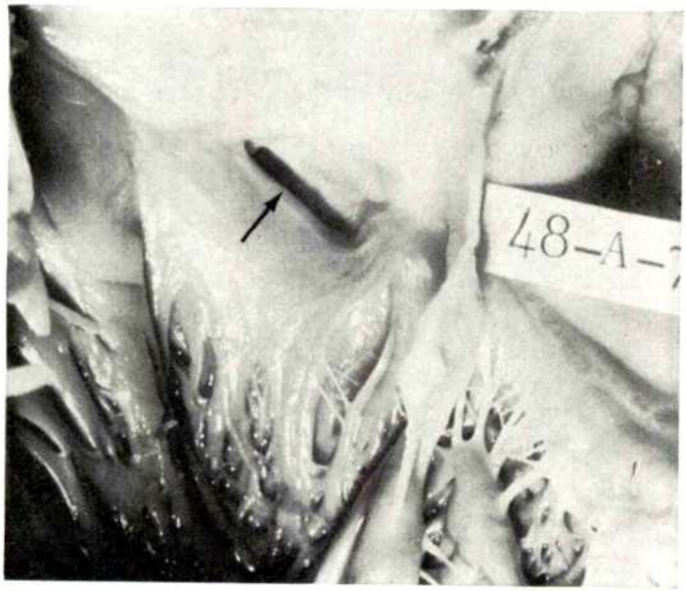


(*c*)

Fig. 19 (*a*) *Left ventricular angiogram from a 4-year-old boy with severe cyanosis. The defect was vertical and low in the muscular septum (arrow) which was confirmed at necropsy.* (*b*) *Left ventricular angiogram showing a closing window type of VSD (arrow) in a 14-year-old girl with tricuspid atresia who developed hypoxic symptoms first at age 5 years.* (*c*) *Window type of VSD (arrow) in a child aged 10 years with tricuspid atresia, showing signs of closing. Same anatomy as patient shown in 19b.*

flow may develop in more complex cardiac anomalies if muscle bands encircling an abnormally placed outflow tract become hypertrophied, such as that seen in some forms of univentricular hearts without an outflow chamber (Fig. 16) or with a subpulmonary chamber and normally related great arteries (Holmes heart) where the obstruction may occur in the bulboventricular foramen (Somerville *et al.*, 1975). The same process operates in tricuspid atresia with normally related great arteries. As the bulboventricular foramen (or ventricular septal defect) through which the left ventricle communicates with the right ventricular outflow tract shrinks, the pulmonary blood flow diminishes.

Newborns with uncomplicated tricuspid atresia usually have a normal-sized pulmonary artery and a large ventricular septal defect (Kreutzer *et al.*, 1973). In the absence of pulmonary valve stenosis or atresia the size of the VSD controls the size of the pulmonary blood flow and the symptomatic state in these patients. In the early months of life babies with tricuspid atresia may present with heart failure and increased pulmonary blood flow and later cyanosis appears as the hole shrinks.

In order to find how frequently this morphological change influenced the natural history of tricuspid atresia, the age when hypoxia first developed in 74 children with tricuspid atresia and normal great arteries was studied (Fig. 17). The few patients with added pulmonary atresia or valve stenosis are shown. It can be seen that the majority had no pulmonary valve lesion and reduced pulmonary flow and hypoxia was thus the result of reduction in the size of the VSD (bulboventricular foramen), the importance of which was first recognised by Brock (1964).

It can be deduced from seeing the different ages when the patients with tricuspid atresia presented with hypoxia that the behaviour of the VSD varies. This must, as in uncomplicated VSD, be related to the basic anatomy. In tricuspid atresia the inflow portion of the right ventricle with the medial papillary muscle is absent and so the classification used in simple VSD cannot be applied in tricuspid atresia. For simplicity the defects in tricuspid atresia will be described as viewed from the left ventricle. In a necropsy study of 60 hearts there were two main types of defect (L. Becú, 1976, personal communication); either 'low' in the muscular ventricular septum surrounded by muscle (Fig. 18a) or more often cephalad where they appeared as an oval window separated from the aortic valve by a muscular band (Fig. 18b). It appeared that the lower defect, depending on its initial size, critically reduced in size (Fig. 19a) earlier than the window type nearer to the aortic valve (Fig. 19b and c). Complete closure of both types was documented in 7 patients whose lives were prolonged by palliative procedures. In 2 patients with closing of the cephalad type, subaortic stenosis developed with gradients of 35 mmHg and 45 mmHg, respectively. This appeared to be the result of hypertrophy of the superior muscle band (Fig. 20) which probably occurred as part of the progressive left ventricular hypertrophy. This complication was bad in patients who were presented for Fontan procedures and must be considered in the assessment of patients for this type of operation.

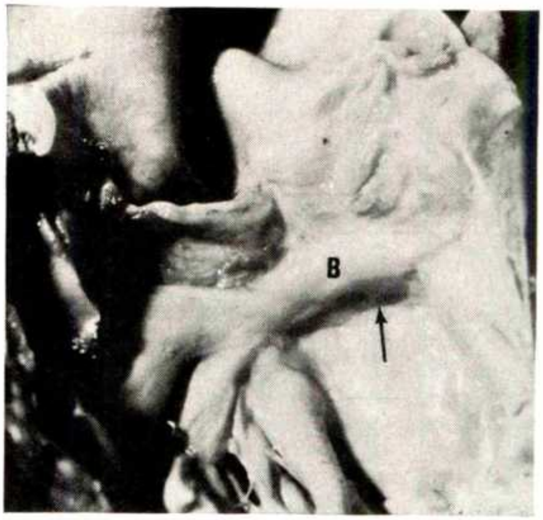


Fig. 20 *Heart viewed from the left ventricle from a boy aged 17 years who had palliative surgery for tricuspid atresia at age 6 years and died after a modified Fontan procedure. The window type VSD has closed spontaneously but hypertrophy of the muscular bar (B) above the defect has caused mild subaortic obstruction with a gradient of 35 mmHg. Arrow shows where VSD has closed.*

It was rare for the 'VSD' in tricuspid atresia with normal great arteries to remain large throughout postnatal life and be associated with persistent pulmonary hypertension. Thus, banding of the pulmonary artery in such infants in failure with tricuspid atresia is probably contraindicated in view of the natural history.

Once the VSD (bulboventricular foramen) reduces in size and limits flow, the once normal right outflow and pulmonary arteries will not grow. If this occurs early these hypoplastic structures cannot be used in these modifications of Fontan operations and so this change in morphology must be considered in the management of such patients.

Acquired left ventricular obstruction in normally placed outflow tracts

Obstruction can also develop in the left ventricular outflow tract appearing as a fibrous ring, rarely described as a membrane. The fibrous obstruction is usually eccentric, attached to the anterior cusp of the mitral valve, and usually associated with severe septal hypertrophy. This type of collagen tissue is not found in newborn hearts, presumably because there is no turbulence in the fetal heart and this lesion has never been reported to cause death under 1 year. There are, therefore, grounds to consider that this 'fixed' subaortic obstruction is thus acquired and not congenital. However, despite its probable absence in the newborn, I believe that fixed subaortic obstruction develops in relation to the presence of some congenital abnormality perhaps in the cardiac muscle. In a consecutive series of 39 patients with fixed subaortic stenosis other congenital lesions in the cardiovascular system were present in 22 (56%); this supports the likelihood of the influence of some congenital disorder in the aetiology.

Perhaps more relevant is that as well as simple myocardial hypertrophy in the left ventricle areas of myocardial dysplasia identical to hypertrophic obstructive cardiomyopathy (or asymmetrical septal hypertrophy) are present low in the ventricular septum in infants who die from other diseases in whom mild fixed subaortic stenosis has been found (L. Becú, 1976, personal communication). After complete surgical removal of the fixed part of the obstruction leaving only small pressure gradients across the left outflow at rest, the left ventricle responds to inotropic stimuli and ectopic beats as if hypertrophic obstructive cardiomyopathy were present in many patients, suggesting that the muscle is very abnormal (Somerville and Montoyo, 1971; Somerville and Becú, 1977). Perhaps this abnormal muscle in the septum contracts abnormally, develops secondary changes and causes turbulence in the abnormal outflow, and stimulates the formation of fixed subaortic stenosis which in turn further stimulates the abnormal muscle.

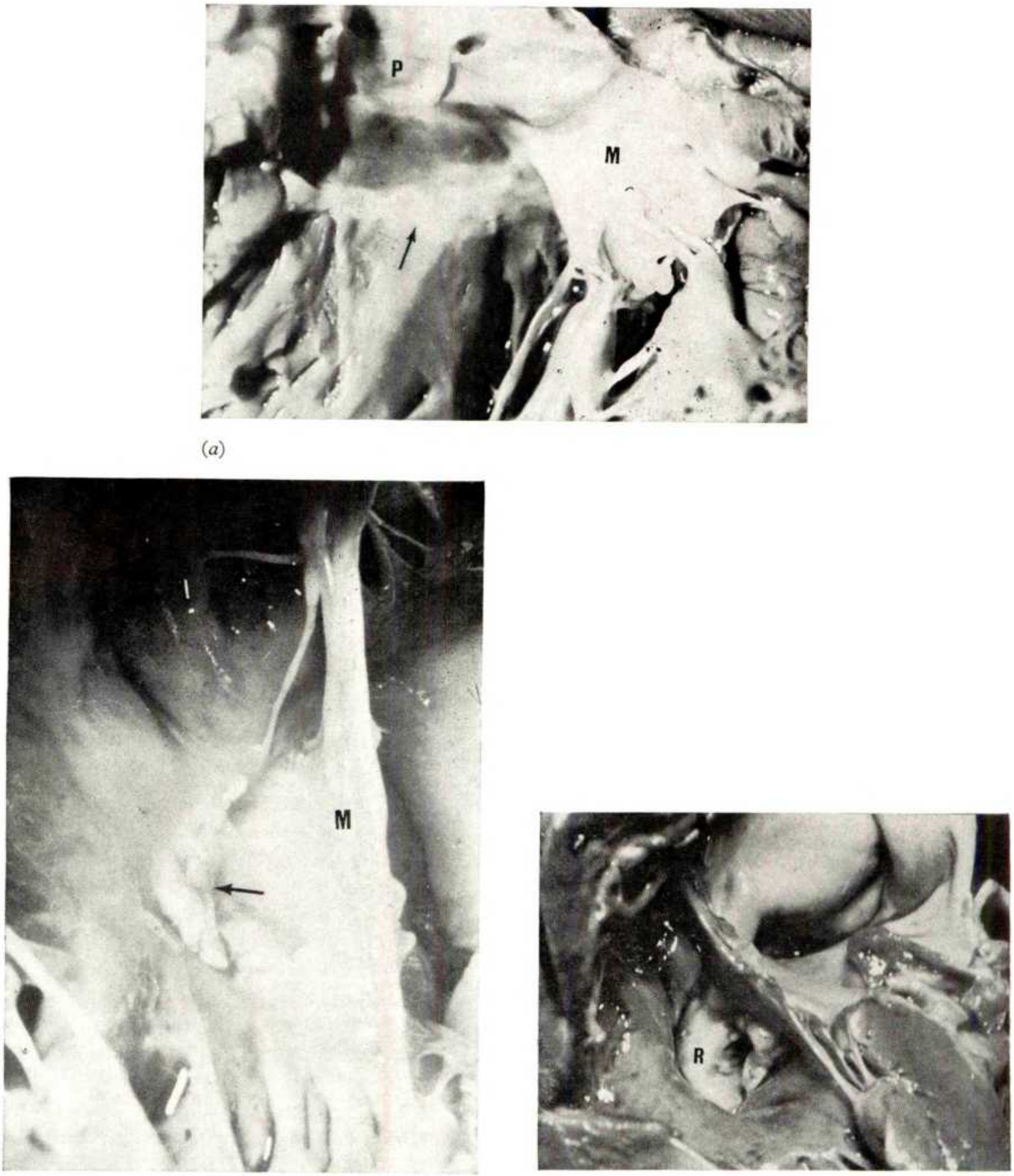
This type of fixed subaortic stenosis may also form with certain ventricular septal defects anterior to the medial muscle of the tricuspid valve. If the subaortic obstruction is not recognised when the ventricular septal defect is closed from the right ventricle the patient may die from untreated left ventricular outflow obstruction. Sometimes a fixed subaortic stenosis forms as a VSD closes spontaneously.

The subpulmonary obstruction from the accumulation of fibrous tissue in the left ventricular outflow tract in certain patients with classic transposition of the great arteries (TGA) is also acquired, not congenital, when it has the same anatomical and histological form as the fixed subaortic stenosis described above. Its presence limits pulmonary blood flow, increasing the central cyanosis in TGA, adding signs of pulmonary stenosis, and increasing left ventricular hypertrophy. The opportunity to examine the left ventricular outflow stenosis presents earlier in transposition than in fixed subaortic stenosis and thus we know more about its pathogenesis.

The obstruction begins as a deposition of fibrous tissue on the ventricular septum opposite the anterior mitral cusp (Fig. 21a). This fibrous area becomes crescentic and eventually forms a complete ring (Fig. 21b and c). Careful histological sectioning of the ventricular septum beneath these obstructions in 5 such patients, aged 5 months to 20 months at the time of death, has shown dysplastic myocardium (Somerville and Becú, 1977) but we do not know how much muscle dysplasia must be present to be associated with significant obstruction or why only some patients develop it. The speed and extent at which left ventricular outflow obstruction develops in transposition must depend upon factors other than the presence of dysplastic muscle in the ventricular septum, such as abnormal septal movement and altered haemodynamics, particularly left ventricular hypertension associated with an added lesion. There are other anatomical forms of subpulmonary obstruction in TGA but this ring form is the most common. It is easily removed during arterial correction for transposition (Ross *et al.*, 1976), but we do not yet know whether it continues to progress when the aorta is restored to its correct position.

Acquired subaortic obstruction in complex anomalies

Subaortic stenosis can develop as the bulboventricular foramen ('VSD') shrinks in certain complex anomalies. This may occur in some univentricular hearts with a subaortic chamber (Somerville *et al.*, 1974) or subaortic conus, tricuspid atresia with transposition particularly when associated with coarctation, double outflow right ventricle (Fig. 22a and b), and occasionally in classic transposition (Fig. 23a and b) where the anterior aorta is connected to the physiological and anatomical right ventricle. The formation of such an obstruction



(*a*)

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Fig. 21 *Formation of subpulmonary obstruction in classic transposition of the great arteries (TGA). (a) From a baby aged 5 months who died after a Mustard procedure. Viewed from the left ventricle, the start of a fibrous ridge on the ventricular septum can be seen forming (arrow) opposite the mitral anterior cusp (M) and beneath the pulmonary valve (P). A gradient of 5 mmHg had been recorded between pulmonary artery and left ventricle. (b) Crescentic obstructing ridge on ventricular septum in a 4-year-old child with TGA and ventricular septal defect, viewed from the apex of the left ventricle with anterior cusp of the mitral valve to the right (M) and subpulmonary ridge on the left (arrow). (c) Fully developed fibrous (collagen) subpulmonary ring obstruction (R) in the left outflow in a 6-year-old patient with TGA, viewed from the apex of the left ventricle.*

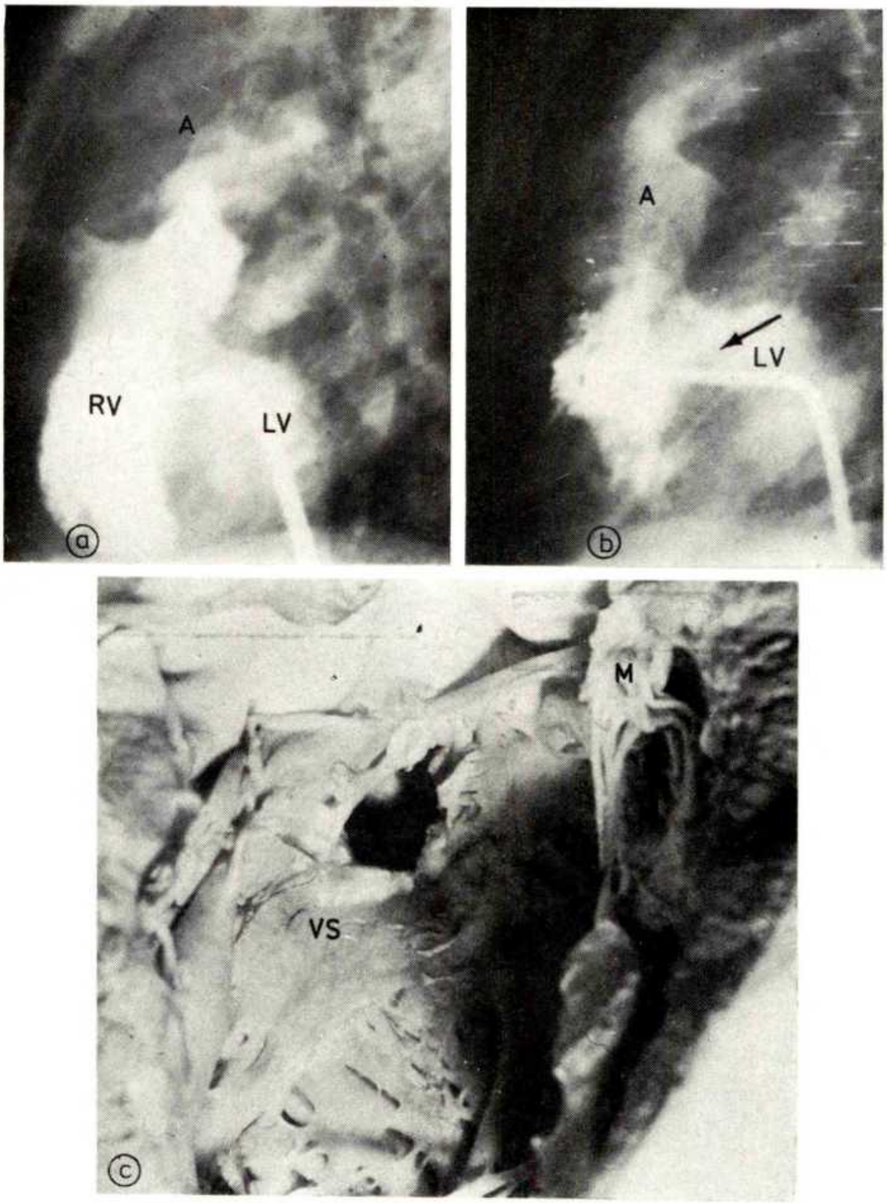
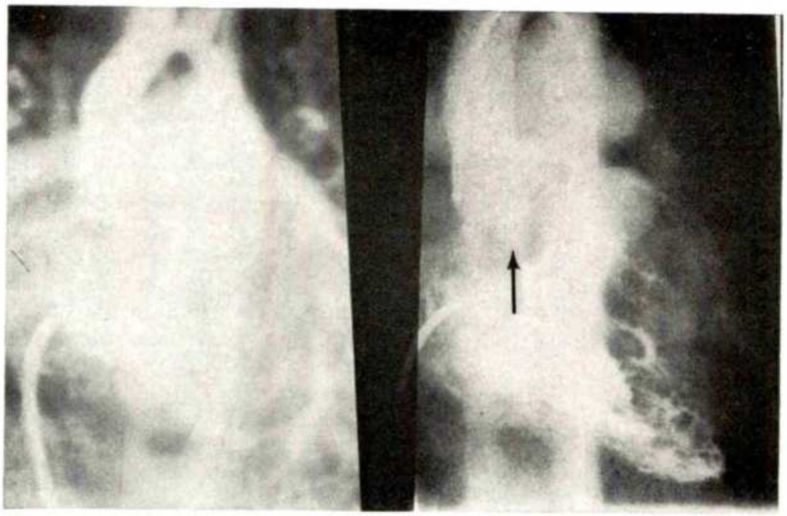


Fig. 22 *Serial right ventricular angiograms from a patient with double outflow right ventricle and pulmonary stenosis. (a) At age 4 years, the left ventricular pressure was 10 mmHg above the aortic pressure. (b) At age 15 years, the left ventricular pressure (165/0 mmHg) was 75 mmHg higher than the right ventricular pressure and fibrous lips can be seen around the defect (arrow). A, ascending aorta; RV, right ventricle; LV, left ventricle. (c) Ventricular septal defect in double outflow right ventricle, viewed from the left ventricle. Between mitral cusp (M) and ventricular septum (VS) is a fibrous ring around the VSD. A systolic gradient of 75 mmHg was present between the left ventricle and the right ventricle.*

depends upon the distribution of the displaced muscular bands and how quickly enlargement takes place in them. Banding of the pulmonary artery may accelerate the development of this obstruction (Freedom *et al.*, 1977) and should not be done as a palliative procedure when the anatomic potential



(*a*) (*b*)

Fig. 23 *Serial angiograms from a child with TGA, VSD, and coarctation who developed severe subaortic obstruction from hypertrophy of displaced bands in the right ventricle beneath the aortic valve. (a) Age 3 months, before resection of coarctation. Bands visible beneath the aortic valve. Right ventricular pressure 10 mmHg above the ascending aortic recorded pressures. (b) Age 4 years, 3 years after resection of coarctation and banding of the pulmonary artery. There was a gradient of 100 mmHg between the ascending aorta and right ventricle. The increase in the size of the bands forming the subaortic obstruction is recognisable (arrow).*

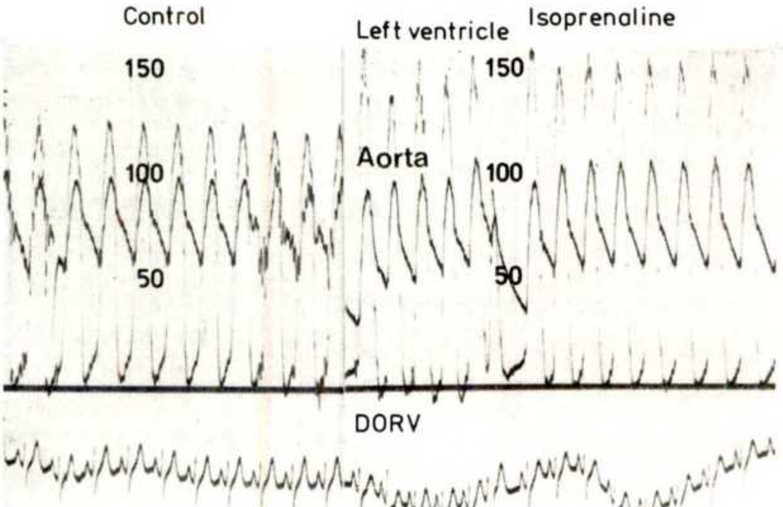


Fig. 24 *Left ventricular and aortic pressures in a 7-year-old boy with double outflow right ventricle and pulmonary stenosis. At rest there was a gradient of 28 mmHg. After isoprenaline the gradient rose to 60 mmHg and the postectopic beat showed an increase in gradient with falling of the aortic pressure as in a labile muscular obstruction.*

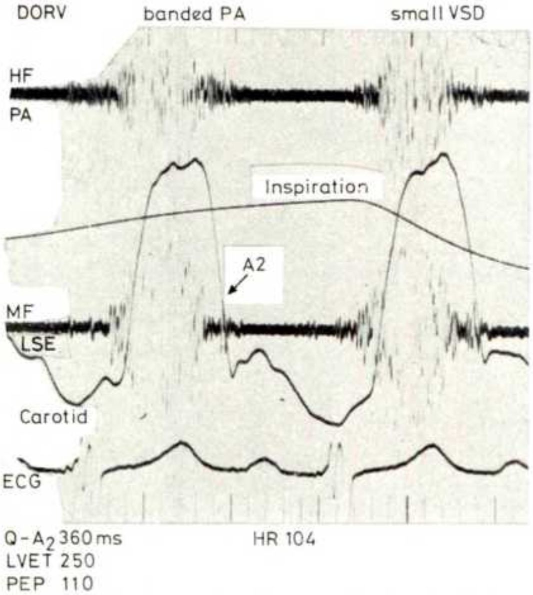


Fig. 25 *Phonocardiogram from an 11-year-old child with severe subaortic stenosis caused by shrinkage of the VSD in double outflow right ventricle. The gradient between the ventricles was 100 mmHg. Aortic valve closure (A2) was diminished with slight prolongation of ejection times.*

for subaortic stenosis to develop is recognised. Both clinicians and investigators must be aware of this serious complication and routinely search for gradients when studying patients, particularly those with one ventricle L-malposition and a subaortic chamber, tricuspid atresia with transposition, and double outflow right ventricle. The documentation of small gradients is important since they may increase with the use of isoprenaline (Fig. 24) and adversely affect the postoperative course. They also increase with time to influence both symptoms and left ventricular function.

The presence of important acquired subaortic stenosis should be suspected clinically if a child with one of these complex malformations develops angina, effort giddiness, or syncope. Aortic valve closure (A2) which is normally loud in many of these pathological complexes, owing to the anterior position of the aorta, may become diminished and even delayed with the appearance of a new carotid thrill (Fig. 25). Adding to the difficulties of clinical assessment is the fact that after banding of the pulmonary artery a thrill in the carotid area is often felt. Unexpected severe left ventricular hypertrophy may develop over the years in double outlet right ventricle with stenosing 'VSD' but this is not seen in univentricular hearts. In double outflow right ventricle the surgeon must be warned of even mild obstruction between the left and right ventricles since a fibrous lip may lie on the left ventricular side of the VSD (Fig. 22c) and may remain untouched by the corrective surgery in the right ventricle and so may progress later. The VSD in double outflow right ventricle which obstructs is the one surrounded by muscle, well separated from the aortic and pulmonary valves and often 'uncommitted' to either. Subaortic obstruction can also develop in double outflow right ventricle from muscular bands within the right ventricle beneath the aortic valve (subaortic conus) which enlarge and hypertrophy.

In all cases seen with this problem, the potential for its development has usually been ignored and retrospective scrutiny of the early investigations has shown the presence of appropriately displaced muscle bands around the foramen, subaortic region, or circling the ventricular septal defect.

Other postnatal pathological changes

The other basic pathological mechanisms which change the cardiac form and function deserve brief mention. Firstly, atrioventricular valve regurgitation either on the right or left side of the heart may be acquired causing failure in sinus rhythm in univentricular hearts, double outflow ventricles, atrioventricular defects, and classic or corrected transposition. This may lead to atrial fibrillation, usually after the first decade, and a downhill course. The natural history of treated and untreated classic transposition may be affected by the onset of tricuspid regurgitation which results mainly from the congenital morphological abnormalities of the tricuspid valve and its attachments (Fig. 26). The abnormal tricuspid valve subjected to high pressures and unusual stresses, particularly when a VSD is present, is liable to rupture, calcification, and fibrosis. In 20 per cent of Rastelli procedures for TGA in patients aged 14 to 30 years in the National Heart Hospital the valve has had to be replaced. Tricuspid regurgitation is a serious complication in a Mustard's operation and encouraged by leaving the right ventricle working at systemic pressures. Whether this will affect those who have had arterial correction must await long-term studies.

Another common pathological ageing change is calcification which affects congenitally abnormal semilunar and atrioventricular valves. Calcification of the congenitally abnormal aortic valve is inevitable and common but its timing depends upon the severity of the obstruction, athletic activities,

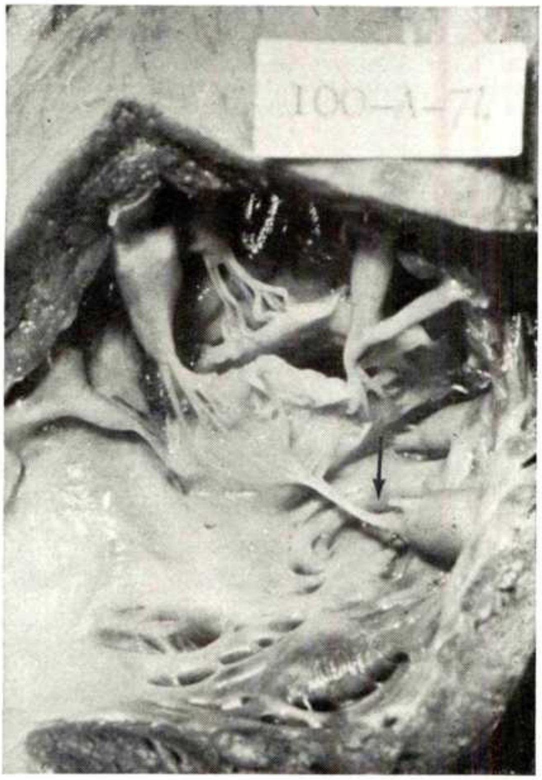


Fig. 26 *Undersurface of tricuspid valve and attachments from a child aged 4 years with TGA and Rashkind septostomy who had a successful Mustard operation one year previously and died from sudden pulmonary oedema. The papillary muscles and chordae are abnormal and one has ruptured (arrow).*

metabolic disturbances, and infection. The congenitally stenosed pulmonary valve also calcifies eventually and features of pulmonary regurgitation usually develop when this occurs. The stenosed pulmonary valve calcifies earlier in adults with cyanotic congenital heart disease and calcium may also be deposited on the tricuspid valve and ring in adults with unrelieved congenital pulmonary valve stenosis. Identification of the calcified pulmonary valve on the chest *x*-ray film of the adult with cyanotic heart disease may aid the correct clinical diagnosis.

Conclusions

Knowledge of the relation between changing form and function must underlie any understanding of the natural history of congenital heart disease. The same principles apply to all forms of heart disease.

Such clinico-morphological correlations were first established in human pathology by Theophilus Laennec (1781-1862) who not only invented the first noninvasive instrument, the stethoscope, but also confirmed his findings by performing necropsies on his patients.

Since then our knowledge of how function alters in response to changing form has been greatly extended by electrocardiography, angiography, radioisotope scanning, and echocardiography. Prolonged survival, often the result of heroic surgery, has added a new dimension of time to our studies of congenital heart disease. What Laennec discovered at necropsy we can now detect in the living and, though Laennec could not follow the changing anatomy by recording the changing physiology as the patients live, we can and must.

I have used congenital heart disease as a model for the study of changing form and function. Correlating the two is the basis of modern cardiology. Progress in medical understanding and surgical dexterity has produced a new medical community, namely the survivors of congenital heart disease. Correct management of these is not ideal unless the predictable effects of changing cardiac form and function for each anomaly are understood within the framework of time.

Some of these ideas were first expressed in an invited talk on 'changing morphology in congenital heart disease' at the World Congress of Cardiology, 1974, and subsequently in the first Stacy White Lecture, Atlanta, 1975.

I am particularly grateful to Luis Becú, Chief of the Department of Pathology, Hospital de Ninos, Buenos Aires, for all the pathological illustrations shown here and for teaching me much about basic morphology in congenital cardiac anomalies. I am indebted to Donald Ross for encouragement, instruction in living anatomy, and many special biopsies, and to the radiologists, Simon Rees and the late Dr Keith Jefferson.

To my associates in the Thoracic Unit, The Hospital for Sick Children, Dick Bonham-Carter, David Waterston, James Taylor, and Fergus Macartney, I am specially grateful for the opportunity to follow survivors with congenital heart disease, and for allowing me access to patients with large ventricular septal defects and tricuspid atresia. I am indebted to James Taylor for Fig. 11b.

Finally, I cannot adequately express my thanks to the teachers who profoundly influenced my thinking, Lord Brock, the late Dr Evan Bedford, and the late Dr Paul Wood.

P, 25, 722

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Haemostatic defects in cyanotic congenital heart disease

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SUMMARY An investigation of defects of the haemostatic mechanism in 41 children with cyanotic congenital heart disease concluded that such abnormalities were common and normally involved factors synthesised in the liver, that is the vitamin K dependent factors (prothrombin, factors VII and IX) and factor V. No evidence was found of activation of the coagulation or fibrinolytic systems. The defects can be explained by deficient synthesis resulting from systemic hypoxia as well as from sluggishness of the local microcirculation caused by high blood viscosity. Vitamin K parenterally had no demonstrable effect. Replacement of these factors, possibly combined with measures to improve the microcirculation, therefore, appears to be the appropriate treatment.

Over the past 25 years multiple defects of haemostasis involving platelet function and the coagulation and fibrinolytic systems have been reported in children with cyanotic congenital heart disease. These have been reviewed by Ekert *et al.* (1970), Maurer (1972), and Wedemeyer *et al.* (1972). Cardiac catheterisation and surgery are prone to be complicated by thrombosis, haemorrhage, or both (Bahnson and Ziegler, 1950; Berthrong and Sabiston, 1951; Hartmann, 1952), and cerebral lesions are an additional hazard (Cottrill and Kaplan, 1973; Terplan, 1973).

This study attempts to define these haemostatic abnormalities and to ascertain whether they are caused by activated coagulation within the circulation, by activated fibrinolysis, or by disordered production of coagulation factors.

Patients

Studies were perfomed on 41 cyanotic patients (25 male and 16 female). Their ages ranged from 1 month to 24 years (median 1 year 6 months). Fourteen had Fallot's tetralogy, 21 transposition of the great arteries, and 6 other complex cyanotic cardiac malformations.

BLOOD SAMPLING

Blood was obtained from a central artery or vein via the polyethylene catheter used for angiocardiography. The silicone technique was used and plasma prepared as previously described (Nilsson *et al.*, 1957). Sodium citrate, 3·8 per cent, in a dilution of 1 to 10 was used as anticoagulant. The results were corrected for haematocrit.

The normal ranges were adjusted to the dilution of plasma. Powdered EDTA was added to blood used for measurement of viscosity.

Methods

Factors II, VII, and X, factor V, factor VIII activity (F VIII:C), factor IX activity, and platelet counts were determined as previously described (Nilsson *et al.*, 1961). Factor VIII antigen (F VIIIR:Ag) was determined with Laurell's electroimmunoassay technique (Holmberg and Nilsson, 1973). Fibrinogen was measured as described by Nilsson and Olow (1962) and with the immunochemical method of Karaca *et al.* (1971). Fibrinolytic activity was measured on unheated bovine fibrin plates as described by Nilsson and Olow (1962). Plasminogen was determined by an immunochemical method (Ganrot and Niléhn, 1968). The ethanol gelation test described by Godal *et al.* (1971) was used as a test for fibrin monomers. Fibrin/fibrinogen degradation products were determined with the immunochemical method of Niléhn (1967). The determinations of fibrin/fibrinogen degradation products were made on serum obtained from blood collected in tubes containing thrombin and epsilon amino caproic acid. Inhibitors of the fibrinolytic system were determined as described previously (Hedner *et al.*,

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1970). Platelet morphology was studied in a phase contrast microscope. Platelet turnover was estimated with the aid of ^{51}Cr-labelled isologous platelets (Abrahamsen, 1968). Fibrinogen survival was studied with human fibrinogen (AB Kabi, Sweden) labelled with ^{125}I, essentially by the technique of McFarlane (1956). Antithrombin III was determined according to the method described by Abildgaard *et al.* (1970). Fibrinolytic activity in the vessel wall was estimated by Pandolfi's modification of Todd's histochemical method (Pandolfi *et al.*, 1972) on vein biopsy specimens obtained from the chest wall during operation. Whole blood viscosity was measured at 37°C with a Wells-Brookfield cone plate micro-viscometer (Wells *et al.*, 1961). The haematocrit was measured in duplicate with a micromethod. Stained dry blood films were examined for fragmented red cells.

Results

Thrombocytopenia (below 125 × 10^9/l) was found in 6 of the 41 patients, including 4 with a haematocrit of 80 per cent or more (Fig. 1). Factors II, VII, and X were low in 35 of the patients (Fig. 2) and vitamin K (Konakion, Roche, 10 mg intravenously) had no effect on the levels in 10 patients tested. Factor IX was abnormally low in 11 of 22 patients studied (Fig. 2). Factor V was low in 21 of the 41 patients (Fig. 3). Factor VIII:C and factor VIIIR:Ag were normal or increased. Fibrinogen determined by the clot method was decreased in 5 of 40 patients (Fig. 3). Fibrinogen determined immunologically was normal. Fibrinolytic activity on fibrin plates was increased in 3 out of 36 patients examined.

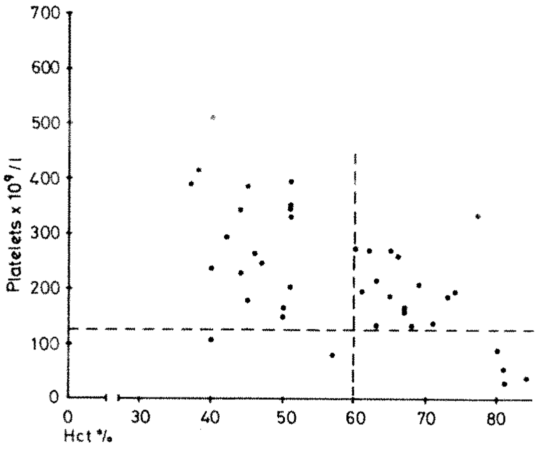

Fig. 1 *Relation between platelet counts and haematocrit.*

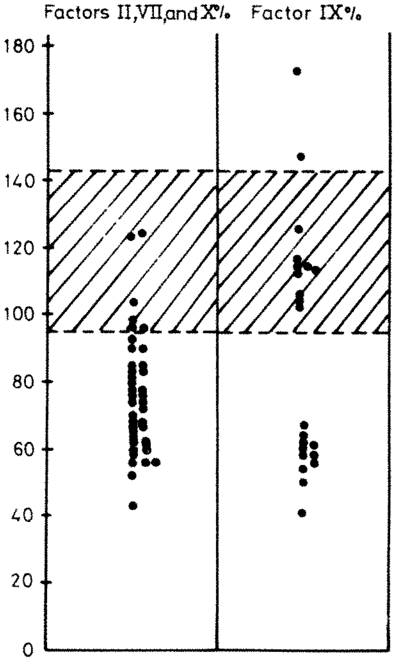

Fig. 2 *The distribution of factors II, VII, and X and of factor IX. Shaded area denotes normal range.*

Fibrin/fibrinogen degradation products occurred in small amounts in 9 of the 41 patients (range 6 to 15 mg/l). Plasminogen, α_2-macroglobulin, and anti-

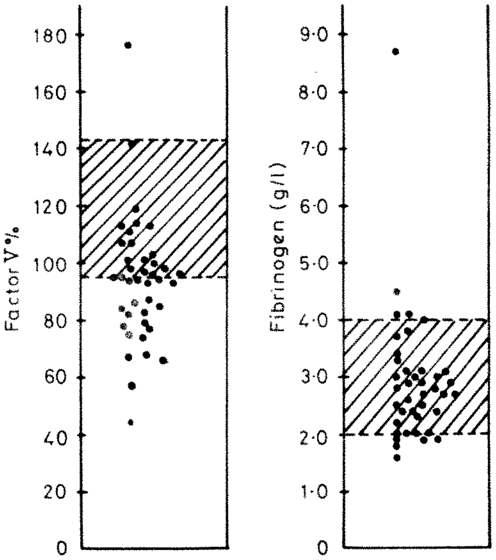

Fig. 3 *The distribution of factor V and fibrinogen. Shaded area denotes normal range.*

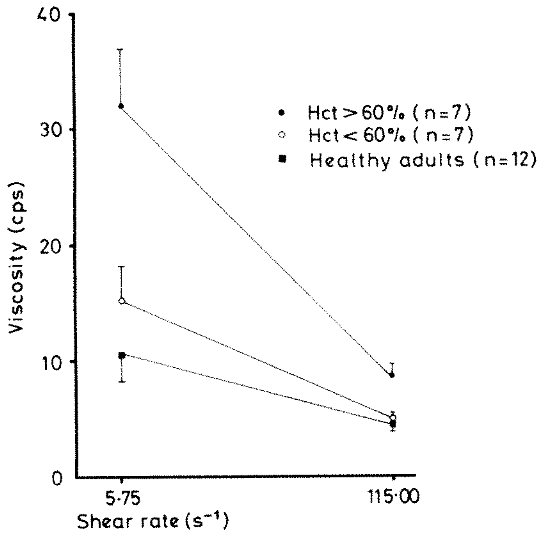

Fig. 4 *Whole blood viscosity in patients with haematocrits above 60 per cent (●), below 60 per cent (○), and healthy adults (■).*

thrombin III were within normal limits. Of 36 patients examined with the ethanol gelation test 3 showed positive results, but 2 of these later became negative. No fragmented red cells were found in 24 patients studied. The appearance of the platelets, including their spontaneous aggregation, adhesion to glass surface, and spreading phenomenon, was normal in 7 patients examined, 4 of them having a haematocrit above 60 per cent. Platelet kinetics and fibrinogen kinetics were studied simultaneously in 5 patients and fibrinogen kinetics alone in 1. The platelet turnover was normal (half-life 3·5 to 4·0 days) in all the 5 patients. The fibrinogen half-life ranged from 1·5 to 3·4 days, mean 2·4 days (normal value found with the same preparation in 8 healthy adults: 3·6 ± 0·4 days). Fibrinolytic activity of the vessel walls in vein biopsy specimens from 8 patients ranged from 5·5 to 9·0 arbitrary units (mean 7·3 units, SD ± 1·4) (values found in 57 healthy children aged 1 month to 13 years: 6·9 units, SD ± 1·7).

Measurements of the viscosity of the blood in 14 patients are given in Fig. 4.

No difference was found in platelet count, fibrinogen, factors II, VII, and X, or factor V between patients above and below 3 years of age.

Discussion

Multiple defects in the haemostatic mechanism in patients with cyanotic congenital heart disease were found, mainly low levels of the vitamin K dependent factors, as indicated by low factors II, VII, and X (85% of the patients) and low factor IX (50%). In addition, factor V was low in 50 per cent of the patients. Thrombocytopenia (below 125 × 10^9/l) was found in only 15 per cent and was associated with high haematocrit levels (Fig. 1): although there is general agreement that such changes occur, opinions differ as to how they should be interpreted. Several workers believe that the abnormalities are caused by activated coagulation within the circulation (Ferencz, 1960; Kontras *et al.*, 1966; Dennis *et al.*, 1967; McKay, 1969; Bleyl and Höpker, 1970; Komp and Sparrow, 1970; Perlick *et al.*, 1971; Ihenacho *et al.*, 1973; Inglis *et al.*, 1975); others by increased fibrinolysis (Gans and Krivit, 1962; Brodsky *et al.*, 1969; Gralnick, 1970; Pike *et al.*, 1975); and some by impaired production of the factors in question (O'Neill and Hutton, 1966; Johnson *et al.*, 1968; Ekert *et al.*, 1970; Iölster, 1970; Maurer, 1972; Wedemeyer *et al.*, 1972). The normal platelet survival and the normal platelet morphology in our patients do not lend support to the hypothesis of increased consumption. A shortened platelet life-span has, however, been shown by other workers (Kummer *et al.*, 1964; Wedemeyer and Lewis, 1973; Goldschmidt *et al.*, 1974; Waldman *et al.*, 1975). The thrombocytopenia might be explained by a hypoxic inhibition of platelet production (Gross *et al.*, 1968). The absence of demonstrable fragmented red cells argues against fibrin deposition within the vessels. Fibrin/fibrinogen degradation products appeared in very small amounts in 25 per cent of the patients. Increased fibrinolytic activity was found in a few patients only, but the plasminogen concentrations were normal and the fibrinogen concentration was decreased in only 13 per cent. Yet the fibrinogen half-life was slightly shortened, while the platelet half-life measured at the same time was normal, indicating an increased catabolic rate of fibrinogen rather than a conversion to fibrin. No discrepancy was found between F VIII:C and F VIIIR:Ag (Henriksson and Holmberg, 1978). F XIII was normal (Hedner *et al.*, 1975) and AT III as well as the α_2M were normal. The overall picture, then, suggests that intravascular proteolytic activity with activation of the coagulation and/or the fibrinolytic systems is unlikely to be a cause of the haemostatic disturbances in these patients. This raises doubts whether heparin or fibrinolytic inhibitors are of value.

Low levels were found only of those factors known to be synthesised in the liver, that is prothrombin, factor V, and factor IX. Thus the abnormality is more consistent with that seen in impaired liver function. Evidence of liver damage in hypoxia has been presented by Ghosh and Emery (1973) and has also been discussed by Wedemeyer *et al.* (1972). The appearance of fibrin/fibrinogen degradation products in low concentrations could be explained by reduced elimination consequent upon reticuloendothelial dysfunction. Low levels of factors II, VII, and X could not be corrected by parenteral administration of vitamin K; this is consistent with the observation that hypoxic liver damage prevents the synthesis of prothrombin complex from vitamin K (Markarian *et al.*, 1967; Appleyard and Cottom, 1970). Goldschmidt (1970), however, did note a rise in prothrombin complex after administration of vitamin K. According to Isacson and Nilsson (1972) patients with recurrent thrombosis often have a reduced fibrinolytic activity in their vessel walls. Our patients were normal in this respect. Thrombotic complications might, therefore, be explained on haemorheological grounds, such as the high blood viscosity reported by Kontras *et al.* (1970), by Ohshima (1976), and also found in our patients.

If impaired production of coagulation factors and platelets is, in fact, the cause of the multiple haemostatic defects in patients with cyanotic congenital heart disease, it may be worth trying preoperative replacement therapy with platelets and preparations of factor IX concentrates, such as Preconativ (Kabi, Sweden), which also contains prothrombin and factor VII and is not thrombogenic (Hedner *et al.*, 1976), together with methods to improve the microcirculation.

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Location and vascular supply of sinus node in human heart

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SUMMARY The exact location of the sinus node was determined in 25 infant hearts using reconstructive techniques. The sinus node was found to lie on the lateral aspect of the superior cavo-atrial junction in the great majority (22 hearts). In only 3 hearts was it found to straddle the summit of the crest of the right atrial appendage where it is popularly believed to be located. In the majority of instances a single artery supplied the node (in 11 hearts the artery approached posteriorly, and in 10 the artery approached anteriorly), though there was considerable variation in the exact anatomy of the arterial supply. Connections between the sinus node and atrial myocardium were diffuse and abundant but in no instances were tracts of specialised cells observed leaving the node and traversing any distance through the atrial wall. These findings are relevant to the sinus node dysfunction that may follow cardiac surgical procedures.

Increased interest in disorders of sinus node function, together with the known vulnerability of the node to surgical injury, have reawakened the thirst for knowledge of its anatomy, histology, normal ageing changes, and vascular supply. Despite the wealth of published reports describing the anatomy of the node, its exact location is not well appreciated. Though originally described in a lateral position in the sulcus terminalis by Keith and Flack (1907), a finding endorsed by Koch (1909) and several subsequent investigators (James, 1961; Truex *et al.*, 1967; Lev and Bharati, 1974, 1977; Anderson *et al.*, 1978), Blair and Davies (1935), Davies (1942), and Hudson (1965), described the node as straddling the crest of the right atrial appendage at its junction with the superior vena cava. The precise course of the artery of supply to the node is also not fully understood, James (1961) indicating that it may approach the node in either a clockwise or counterclockwise fashion relative to the superior vena cava, while Hutchinson (1978) has described a caval circle of arteries in the environs of the node.

These possible variations are of major significance in postoperative sinus node dysfunction, a problem compounded by controversies surrounding the substrates for internodal atrial conduction (James, 1963; El Said *et al.*, 1972; Isaacson *et al.*, 1972; Janse and Anderson, 1974). With all these considerations in mind, we have attempted to define accurately the anatomy, disposition, connections, and vascular supply of the sinuatrial node by reconstructions from histological sections of 25 normal human infant hearts.

Subjects and methods

The anatomically normal hearts were from infants less than 1 year of age. Infant hearts were used because the smaller tissue block is easier to handle and the borders of the node can be more accurately defined. In each heart the superior vena cava and adjacent atrium were excised. This block was carefully embedded and serially sectioned with the rotary microtome set at 10 μ. Every 25th section was mounted and stained with the Masson trichrome method. Extra sections were prepared as required. In 8 instances the block was sectioned in a frontal plane (anteroposterior) and in 17 instances in a transverse plane (superoinferior) (Fig. 1). The anatomy of the sinus node and its arterial blood supply was then reconstructed on graph paper. With the coronal method of sectioning,

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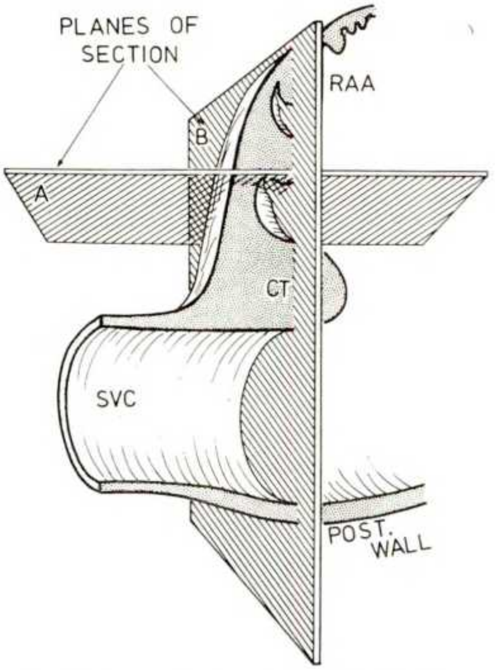

Fig. 1 *Diagram to illustrate the two methods of sectioning the tissue block for histological examination of the sinus node. (A) Frontal plane sectioning (8 hearts). (B) Tranverse plane sectioning (17 hearts). SVC, superior vena cava; RAA, right atrial appendage; CT, crista terminalis.*

reconstruction was carried out with the aid of a calibrated measuring eye piece (Fig. 2).

Results

The sinus node was easily identified in all the hearts studied. Though in several there was venous congestion of the node and adjacent atrial myocardium, no other pathology was recognised.

LOCATION OF NODE

In 22 hearts the sinus node lay in the groove between the right atrial appendage and the lateral atrial wall (sulcus terminalis) (Fig. 3). The long axis of the node was parallel to the sulcus terminalis, with the anterosuperior 'head' situated between 2 and 4 mm below the crest of the right atrial appendage. The posteroinferior 'tail' was up to 10 mm below this level. The anterosuperior 'head' was subepicardial and the posteroinferior 'tail' predominantly intramyocardial with the tip of the 'tail' contacting subendocardial tissue. In 3 hearts the sinus node straddled the crest of the atrial appendage so that the anterosuperior 'head' was to the left of the crest and the 'body' and 'tail' were to the right of the crest (Fig. 4). In these hearts the posteroinferior 'tail' was situated at a higher level than in the other 22 hearts.

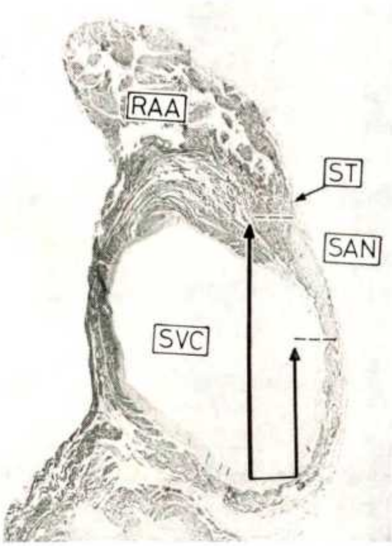

Fig. 2 *A transverse section of the cavoatrial junction showing the sinus node. Examples of some of the measuring lines used to reconstruct the anatomy of the region are superimposed. SVC, superior vena cava; RAA, right atrial appendage; SAN, sinuatrial node; ST, sulcus terminalis.* (× 7.)

DIMENSIONS OF NODE

The node measured between 4 and 6 mm in length, 2 and 3 mm in width, and less than 1 mm in thickness. These measurements did not include the transitional zone around the node (*vide infra*).

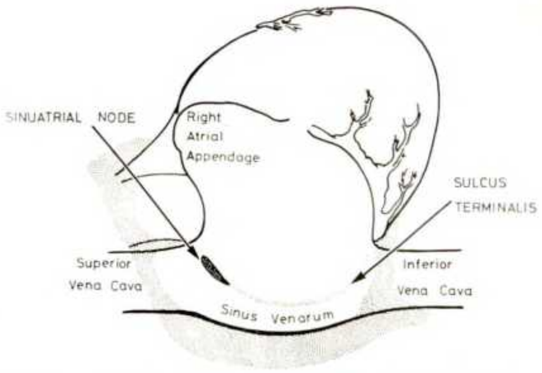

Fig. 3 *Diagram of a heart viewed from the right side of the chest showing the location of the sinus node in 22 of the 25 hearts studied.*

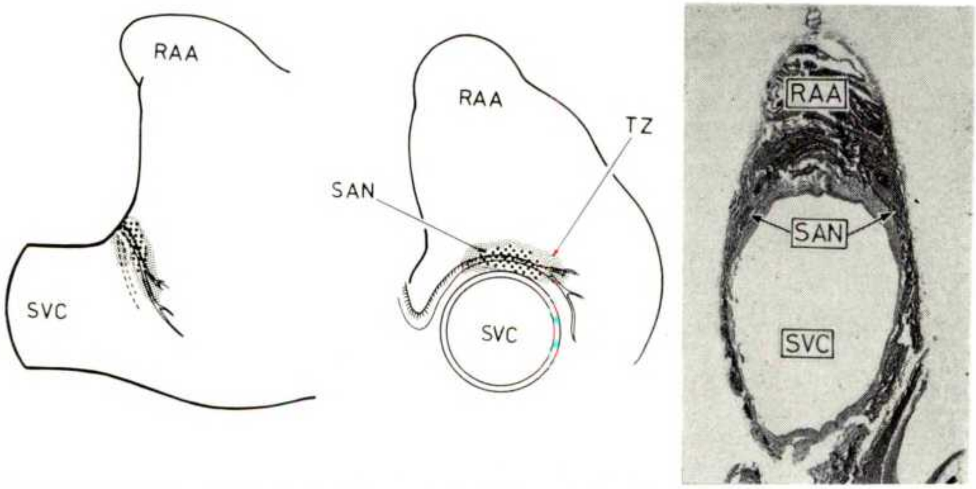

Fig. 4 *The location of the sinus node in 3 of the 25 hearts studied. On the left is a diagram of the cavoatrial region viewed from the right chest. In the centre is a similar diagram but viewed from above the heart. On the right is a photomicrograph (× 7) of a section through the atriocaval junction which shows nodal tissue associated with the sinuatrial node artery. This is situated both lateral and medial to the mid-line crest of the right atrial appendage where it joins the superior vena cava. RAA, right atrial appendage; SVC, superior vena cava; SAN, sinuatrial node; TZ, transitional zone of the node.*

HISTOLOGY AND CONNECTIONS OF NODE

The topography of the nodes showed considerable variation, with tongues of nodal tissue extending centrifugally outwards to accompany branches of the sinus node artery. These tongues did not become connections between nodal and atrial myocardium for they remained surrounded by connective tissue. Cell to cell contact between sinus node specialised cells and atrial myocardial cells was infrequently identified with certainty, though closely approximating cells were often observed. This was seen particularly where the large bulk of muscle making up to the crista terminalis was related to the node and here a transitional zone was present. More posteriorly, towards the tail of the node, nodal cells closely approximated the more sparsely muscularised posterolateral atrial wall. Frequently a small bundle of nodal cells extended in the epicardium some distance posterior to the node.

The infant sinus nodes were predominantly composed of syncytial cells which were randomly orientated and irregularly interlacing. The major bulk of each node was made up of specialised cells but there was always a background framework of fine collagen and reticulin fibres.

ARTERIAL BLOOD SUPPLY

In 11 hearts (44%) the sinus node artery approached the node from the posterior aspect, circling the posterior atrial wall in an anticlockwise direction (looking down at the heart from above). When turning on to the lateral atrial wall the artery was considerably inferior to the level of the summit of the crest of the right atrial appendage and the artery coursed superiorly as well as anteriorly to reach the 'tail' of the node (Fig. 5A). In 10 hearts (40%) the artery approached the node from the anterior aspect, circling clockwise (looking down at the heart from above), and arching over the crest of the right atrial appendage. On reaching the lateral atrial wall the artery coursed posteroinferiorly to reach the 'head' of the node (Fig. 5B). In 4 hearts (16%) arteries approached both anteriorly and posteriorly and anastomosed within the substance of the node (Fig. 5C).

In 8 hearts (32%) the artery ramified and terminated in the node. In 13 hearts (52%) the artery coursed through the centre of the node continuing distally to the atrial wall. In 2 hearts (8%) the major artery skirted the node and in a further 2 hearts (8%) no dominant artery was present.

VENOUS BLOOD SUPPLY

Veins did not accompany the sinus node artery but in several instances small venules from the node were observed draining directly into the right atrium adjacent to the node.

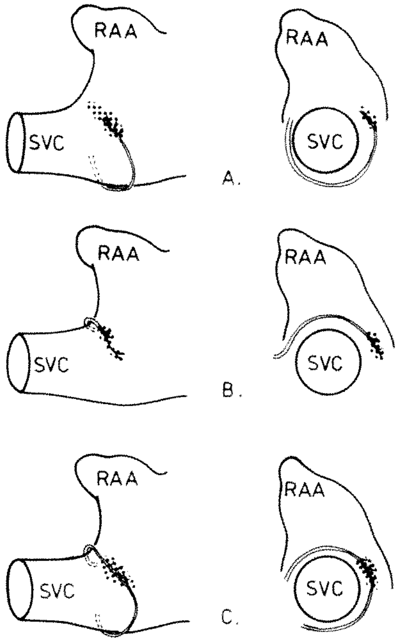

Fig. 5 *Diagrams to illustrate the variable arterial supply of the sinus node. Those on the left of the Fig. are as viewed from the right and those on the right of the Fig. are as viewed from above the heart. (A) posterior approaching artery (11 hearts). (B) anterior approaching artery (10 hearts). (C) anastomotic ring (4 hearts). SVC, superior vena cava; RAA, right atrial appendage.*

Discussion

Our findings regarding the disposition of the sinuatrial node are very much an endorsement of the initial description of Keith and Flack (1907), and the subsequent studies of Koch (1909), and others. In the majority of hearts, therefore, the node was a lateral structure relative to the superior cavo-atrial junction, a finding in contrast to those of Blair and Davies (1935), Davies (1942), and Hudson (1965), who described the sinuatrial node as a structure slung over the crest of the right atrial appendage. However, this variation was observed in 3 of the 25 (12%) normal hearts. With the exception of these cases we found the infant sinus node to be remarkably constant in position. It lies on the lateral right atrial wall with its long axis in the sulcus terminalis, and its anterior 'head' superior to its posterior 'tail'. It is unlikely that the location should be any different in adults.

Variations in the description of the precise position of the sinuatrial node by various authors (Taussig, 1931; Blair and Davies, 1935; Hudson, 1965; James, 1961; Truex *et al.*, 1967; Lev and Bharati, 1974; Anderson *et al.*, 1978), may in part be the result of the limited individual variation in nodal position but seems more likely to be attributable to the method of sectioning the tissue block. When the block is sectioned in a frontal plane, or by the method advocated by Hudson (1965), the sections obtained do not contain an indentifiable reference point to which the node can be related. The transverse method of sectioning has the distinct advantage that the relatively straight posterior caval and atrial walls are seen in every section and provide a constant reference base for morphometric reconstruction.

The topography of the node is also variable, with small tongues of nodal tissue extending outwards to accompany branches of the main artery. Despite this, the basic shape of the node is constant. It is pointed at each end of the long axis and the long axis is two to three times the dimension of the width. It is flattened against the atrial wall but the inferior margin is thicker, so that in cross-section the node appears triangular, with the apex of the triangle directed upwards.

Close encounters between specialised nodal cells and atrial myocardial cells were seen frequently, particularly in the crista terminalis and posterolateral atrial wall. The histology of these regions is distinct, resembling neither the node itself nor the atrial musculature, and the term transitional zone is warranted. Definite cell to cell contacts between specialised cells and atrial myocytes can also be observed, but in no instances have we seen discrete tracts of specialised cells leaving the node and traversing any distance into the atrial myocardium. The latter point is of importance in the sinus node dysfunction that may occur after cardiac surgery, for it has been suggested that this is often the result of interruption of atrial internodal pathways (Isaacson *et al.*, 1972). This seems unlikely in the presence of relatively abundant connections between node and atrium and in the absence of distinct pathways (Janse and Anderson, 1974). In our view it is far more likely that postoperative sinus node dysfunction is the result of either direct trauma to the node or interruption of the arterial blood supply to the node.

An increase in connective tissue in the sinuatrial node is a normal change with age (Lev, 1954), though at any age the quantity of collagen is variable (James, 1961, 1977). The functional significance of this ageing phenomenon is questionable, but Evans and Shaw (1977) found distinct fibrosis of the node in some patients with chronic sinuatrial node disease. The infant nodes in this study all had an identifiable reticulin and fine collagen framework, in contrast to the findings of James (1977). None the less, the bulk of the node was composed of specialised cells. The dimensions were approximately one-half those previously reported for adult nodes (James, 1961; Merideth and Titus, 1968). It is our impression that the increased size of the adult sinuatrial node can be attributed to its increased connective tissue component with corresponding decrease in the proportion of nodal specialised cells per unit area of node, though this observation requires quantitative documentation.

The sinuatrial node artery may approach posteriorly, anteriorly, or less commonly from both directions. We concur with James (1961) that there is considerable variation in the size of the artery and its method of ramification within the node. We do not agree with Hutchinson (1978) that the sinuatrial node artery in the majority of hearts is part of an anastomotic ring around the atriocaval junction and we found this to be the exception rather than the rule. It is possible that the development of an anastomotic ring is an ageing feature as the majority of Hutchinson's subjects were in the fifth and sixth decades and ours were infants.

Thus our findings show that on external examination of the heart, the location of the sinuatrial node can be predicted using the summit of the crest of the right atrial appendage and the sulcus terminalis as landmarks, the node in the majority of cases being a lateral structure. From within the right atrial chamber the crista terminalis, which is the internal expression of the sulcus terminalis, is a satisfactory landmark. The location of the artery supplying the node is less predictable but if surgical injury is to be prevented with certainty, then the entire atriocaval junction should be avoided.

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Postoperative haemodynamics in tetralogy of Fallot
A study of 132 children[1]

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SUMMARY Our study was undertaken to determine the type, incidence, and functional significance of residual anomalies in patients who have undergone corrective repair for tetralogy of Fallot. We reviewed data from cardiac catheterisations performed on 132 survivors.

A significant residual ventricular septal defect was present in only 12 patients. Resting right ventricular systolic pressure was less than 80 mmHg in 100 patients and ranged from 80 to 150 mmHg in the other 32 patients. Thirty-five patients were studied both at rest and during supine exercise. In most patients, the relation between oxygen consumption and cardiac output was normal during exercise. The stroke index and right ventricular end-diastolic pressure at rest and on exercise were compared in 34 patients. Seventeen showed a normal response to exercise. In the other 17 patients, right ventricular end-diastolic pressure rose on exercise; in 5 of these the stroke index fell during exercise, indicating abnormal myocardial response.

Our studies indicate the frequent occurrence of residual abnormalities, even in patients who appear asymptomatic, after total correction of tetralogy of Fallot.

Corrective operations for tetralogy of Fallot were first performed in 1954. Despite extensive experience at a number of centres, the postoperative course of these patients has been described principally in terms of clinical features. Until recently, little information has been available concerning postoperative haemodynamic changes.

We have performed postoperative cardiac catheterisations on 132 survivors of corrective operation for tetralogy of Fallot. This report describes the catheterisation data and the incidence and severity of residual abnormalities. Results of studies made during supine exercise are also included.

Methods

For this report, we define tetralogy of Fallot as a large ventricular septal defect with equal right and left ventricular systolic pressures, coexistent infundibular pulmonary stenosis, normal or low pulmonary arterial pressure, and a systemic arterial oxygen saturation less than 90 per cent. The aorta arose from the left ventricle in all patients, and none had double outlet right ventricle and coexistent pulmonary stenosis. In 118 patients, the pulmonary valve was abnormal, and many of these had a small pulmonary annulus. In the other 14, the pulmonary valve and annulus were normal, and the pulmonary stenosis was related to infundibular stenosis, frequently from anomalous muscle bundles.

One hundred and thirty-two patients with tetralogy of Fallot have been studied postoperatively by cardiac catheterisation. These 132 patients were from a group of 170 patients who survived corrective operation for tetralogy of Fallot. While we recommend postoperative cardiac catheterisation in all patients, 38 patients were not restudied by us, either because they have been lost to follow-up or because they are being followed by their own physician in an area distant from the University of Minnesota. Nineteen patients had had a previous Blalock-Taussig procedure, and 6 others had a Brock operation. None had had a previous total correction for tetralogy of Fallot.

The patients were catheterised in a resting, fasting state after premedication with morphine sulphate and phenobarbitone. Pressure and saturation data were obtained from the right side of the heart to

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detect the presence of a residual shunt or a pressure difference across the right ventricular outflow area. From the data, total pulmonary vascular resistance (TPVR) was calculated according to the formula:

$$\text{TPVR} = \frac{\text{mean pulmonary arterial pressure (mmHg)}}{\text{pulmonary blood flow (l/min)}}$$

Thirty-five patients were studied both at rest and during supine submaximal exercise, using a variable resistance bicycle ergometer set at a work load designed to double the heart rate. The oxygen consumption was measured both at rest and during exercise, and cardiac output was determined by the Fick principle. Expired air was collected in a chain-driven Tissot tank and analysed by the Schonander method. Blood samples were drawn simultaneously from the brachial artery and the pulmonary artery for oxygen analysis by the method of Van Slyke. Pressure was recorded as the catheter was withdrawn through the pulmonary artery, the right ventricle, and the right atrium.

Results

Of the 132 patients, 11 were less than 4 years of age at the time of operation, 89 were 4 to 9 years of age, and the remaining 32 were between 10 and 16 years of age. Seventy-nine patients were restudied between the ages of 4 and 10 years, and 53 between 10 and 18 years of age. Most were studied one year after operation.

RESTING HAEMODYNAMICS

Residual shunt

Studies showed no detectable ventricular septal defect in 106 patients; a residual communication was detected by oximetry in the other 26 (20%) patients (Table 1). A left-to-right shunt between 30 and 50 per cent was present in 14 patients, between 51 and 70 per cent in 7, and greater than 70 per cent in 2. A bidirectional shunt was present in the remaining 3 patients.

Right ventricular systolic pressure

The level of right ventricular systolic pressure was variable (Table 1) and depended upon several factors: the presence of residual right ventricular outflow obstruction, the magnitude of the residual shunt, and the level of pulmonary arterial pressure, which was in turn influenced by the presence of pulmonary regurgitation, the level of pulmonary vascular resistance, and the presence of a stenotic or occluded pulmonary artery. The distribution of peak right ventricular systolic pressures in 54 patients with a patch in the right ventricular outflow tract (30 of these patches being placed across the pulmonary annulus) was no different from the 78 patients without an outflow tract patch.

Excellent relief of the right ventricular outflow obstruction was obtained from operative repair in 79 patients (60%), in whom the peak right ventricular systolic pressure measured less than 60 mmHg. Of these patients, 74 had no residual shunt, and 5 had a left-to-right shunt of less than 50 per cent.

Twenty-one patients (16%) had a right ventricular systolic pressure between 60 and 80 mmHg. Sixteen of these patients had no detectable residual shunt, and in 14 of these the pulmonary arterial systolic pressure was less than 30 mmHg. In these 14 patients, right ventricular outflow obstruction was the cause of the raised right ventricular systolic pressure and the gradient was in the right ventricular outflow tract. In the other 2 patients, the pulmonary arterial systolic pressure was 44 and 46 mmHg, and right ventricular systolic pressures were 70 and 60 mmHg, respectively (Table 2, cases 2 and 6). The remaining 5 patients with right ventricular systolic pressure between 60 and 80 mmHg had a left-to-right shunt, 4 between 30 and 50 per cent and the other 55 per cent. The augmented pulmonary blood flow contributed to their raised right ventricular systolic pressure. In each of these 5 patients, the pulmonary arterial systolic pressure was less than 30 mmHg, and the gradient was in the right ventricular outflow tract.

Thirty-two patients (24%) had a right ventricular

Table 1 *Catheterisation data in 132 children after correction of tetralogy of Fallot*

Right ventricular systolic pressure (mmHg)	*Residual shunt*					*Total*
	None	*Left-to-right (%)*			*Bi-directional*	
		30-50	*51-70*	*> 70*		
< 40	36	2	0	0	0	38
40-59	38	3	0	0	0	41
60-79	16	4	1	0	0	21
> 80	16	5	6	2	3	32
Total	106	14	7	2	3	132

Table 2 *Observations in 13 patients with pulmonary arterial systolic pressure greater than 40 mmHg*

Case no.	*Pulmonary arterial pressure (mmHg)*	*Systemic/pulmonary flow indices (l/min per m²)*	*Pulmonary regurgitation*	*Right ventricular outflow patch*	*Pulmonary arteries*
1	40/16	3·9/3·9	+	+	Normal
2	44/10	4·0/4·0	+	+	Normal
3	44/14	5·2/9·4	+	+	Normal
4	45/11	4·8/7·9	+	−	Normal
5	45/10	2·9/4·0	+	−	Occluded left pulmonary artery
6	46/16	3·8/3·8	+	+	Normal
7	50/10	2·9/6·8	+	+	Normal
8	70/10	4·4/10·1	+	−	Normal
9	70/15	3·7/3·7	+	+	Normal
10	80/20	2·5/7·5	+	+	Normal
11	81/15	3·7/7·5	+	−	Occluded left pulmonary artery
12	90/10	3·3/3·3	+	+	Peripheral pulmonary stenosis
13	95/8	5·5/6·6	+	+	Stenosis right pulmonary artery

systolic pressure more than 80 mmHg, up to 150 mmHg. In only one was the right ventricular systolic pressure above systemic level. Sixteen of these patients had no residual shunt. In 14 of the 16 patients, pulmonary arterial systolic pressure was 30 mmHg or less, and in these patients the raised right ventricular systolic pressure was the result of right ventricular outflow obstruction, usually at pulmonary valve level, but in 2 patients in the infundibulum. In the other 2 patients without a residual shunt, the right ventricular systolic pressures were 85 and 90 mmHg, and pulmonary arterial systolic pressures were 40 and 90 mmHg, respectively (Table 2, cases 1 and 12). Both had a right ventricular outflow patch and pulmonary regurgitation, but in case 12 there was also peripheral pulmonary arterial stenosis.

In the other 16 patients a residual shunt was present; in 8 the shunt was greater than 50 per cent, and in 3 others it was bidirectional. In 8 patients the pulmonary arterial systolic pressure was greater than 40 mmHg (Table 2, cases 4, 5, 7, 8, 9, 10, 11, 13). Though a gradient was measured in the outflow tract, the increased pulmonary arterial pressure made an important contribution to the raised right ventricular systolic pressure. In these 8 patients, the increased pulmonary arterial systolic pressure was associated with increased right ventricular stroke volume, as a result of pulmonary regurgitation and the augmented pulmonary blood flow from a residual shunt. In 2 (cases 5 and 11) this was accentuated by an occluded left pulmonary artery, resulting from bacterial endocarditis in one, and by congenital peripheral pulmonary arterial stenosis in another (case 13).

In the remaining 10 patients with a residual shunt, the pulmonary arterial pressure was less than 30 mmHg in 5, and between 30 and 34 mmHg in the remaining 5. The gradient was in the right ventricular outflow tract in each. The raised right ventricular systolic pressure in these 10 patients was related to a combination of the obstruction and left-to-right shunt.

Thus, 33 of our catheterised patients (25%) had a shunt greater than 50 per cent, or a right ventricular systolic pressure greater than 80 mmHg. The result of the initial corrective operation in these patients was considered unsatisfactory, and a second operation has been performed in 20 to correct residual abnormalities.

Pulmonary arterial pressure

Total pulmonary vascular resistance was normal (less than 3 units) in all but 2 patients. The peak pulmonary arterial systolic pressure was greater than 40 mmHg in 13 patients (Table 2). Pulmonary valvular regurgitation was diagnosed in each of these patients on the basis of auscultatory findings; it was associated with an outflow patch across the pulmonary annulus in 9. Of the 13 patients, 8 had a residual left-to-right shunt and 1 (case 9) a bidirectional shunt, and 4 had either an occlusion or a stenosis of a pulmonary artery.

Of the remaining 119 patients with pulmonary arterial systolic pressure less than 40 mmHg, none had an obstruction or a stenosis of a pulmonary artery. The pulmonary arterial systolic pressure was between 30 and 40 mmHg in 26 of these patients, 24 of whom had auscultatory evidence of pulmonary regurgitation. The pulmonary arterial systolic pressure was less than 30 mmHg in the remaining 96 patients; 53 had clinical pulmonary regurgitation and 43 did not.

Forty-two of the patients with a murmur of pulmonary regurgitation and 11 patients without pulmonary regurgitation had a pulmonary arterial pulse pressure greater than 20 mmHg.

We found no relation between the right ventricular outflow gradient, the presence of a shunt, and the presence of pulmonary regurgitation.

Pulmonary blood flow

At the time of cardiac catheterisation, the pulmonary flow index was less than 3·0 l/min per m² in 90 patients, between 3·0 and 4·5 l/min per m² in 15, and greater than 4·5 l/min per m² in 63. We compared the pulmonary flow index with the level of right ventricular systolic pressure. There was a tendency for patients with a higher pulmonary flow index to have a higher right ventricular systolic pressure, but there were extreme variations because of the varying relative contributions of outflow obstruction and volume of pulmonary blood flow to the height of the right ventricular systolic pressure.

Right ventricular end-diastolic pressure

In patients without pulmonary regurgitation, the right ventricular end-diastolic pressure ranged from 2 to 15 mmHg, mean 6·4 mmHg. Each patient in this group with a right ventricular end-diastolic pressure greater than 10 mmHg also had a right ventricular systolic pressure greater than 90 mmHg. In patients with pulmonary regurgitation, the right ventricular end-diastolic pressure ranged from 4 to 20 mmHg, mean 9 mmHg.

Right ventricular end-diastolic pressure was higher in patients in whom a pulmonary valvotomy was done or an outflow patch was placed (mean 8 mmHg and 9·8 mmHg, respectively) than in those patients who had neither an outflow patch nor a pulmonary valvotomy (mean of 5·4 mmHg), but in part this difference may be related to anatomical differences between those patients with an abnormal pulmonary valve and annulus and those with infundibular stenosis and a normal pulmonary valve.

EXERCISE HAEMODYNAMICS

Thirty-five patients were studied both at rest and during submaximal supine exercise. Cardiac output was measured by the Fick principle. The 35 patients ranged in age from 6 to 16 years. Twenty-six were studied one year after operation, and the other 9 at intervals up to 4 years. Their heart rates ranged from 60 to 105/minute at rest and from 110 to 190/minute on exercise. No patients developed an arrhythmia during exercise.

The cardiac index in each of the 35 patients increased with exercise. The cardiac index during exercise was compared with the corresponding oxygen consumption (Fig. 1). Thirty-one patients showed a normal relation between these two measurements. The cardiac index of the other 4 patients was low in relation to oxygen consumption, indicating impaired cardiac function. Each of these 4 patients had clinical evidence of pulmonary regurgitation and a wide pulmonary artery pulse pressure. Severe residual right ventricular outflow obstruction was also present in 2 of the 4 patients. The third had a small residual ventricular septal defect only. The remaining patient had no residual defect, and his right ventricular systolic pressure was 45 mmHg.

The peak right ventricular systolic pressure increased on exercise in 34 patients (Fig. 2). At rest, the right ventricular systolic pressure ranged from 34 to 105 mmHg; with exercise, the range increased to 38 to 140 mmHg. In the other patient, there was essentially no change.

On exercise, both the peak systolic and the mean systemic arterial pressures increased. In only one patient did right ventricular systolic pressure rise

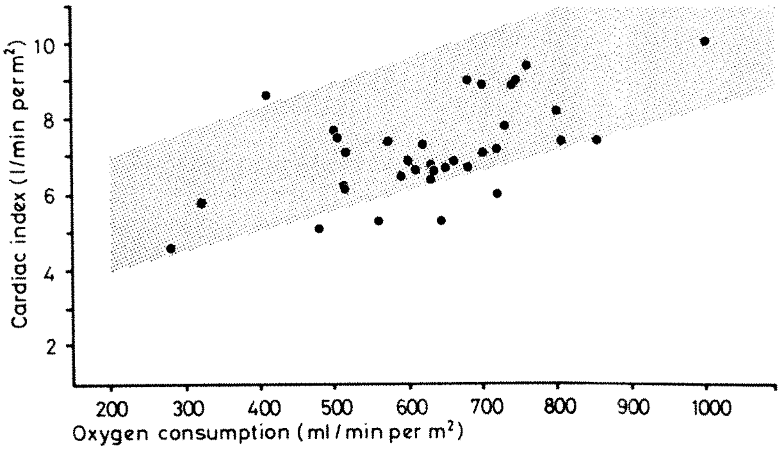

Fig. 1 *Relation between cardiac index and oxygen consumption on exercise in 35 children after repair of tetralogy of Fallot. Shaded area is normal range.*

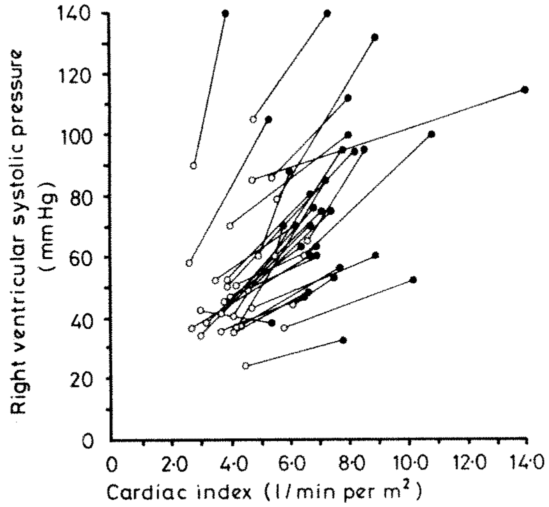

Fig. 2 *Simultaneous change in cardiac index and peak right ventricular systolic pressure from rest to exercise in 35 children after repair of tetralogy of Fallot. Observations on individual patients connected.* ○ = *rest;* ● = *exercise.*

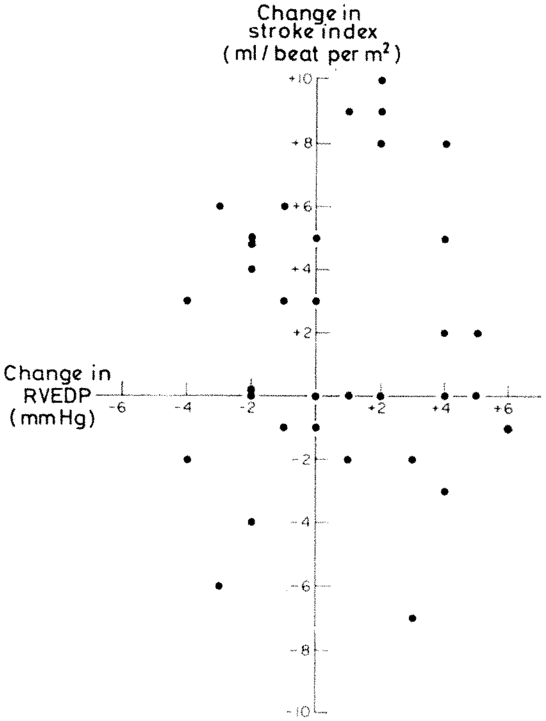

Fig. 3 *Change from rest to exercise of stroke index and right ventricular end-diastolic pressure in 34 children after repair of tetralogy of Fallot.*

above systemic on exercise, and in this patient the peak systolic systemic arterial pressure increased from 110 to 130 mmHg while the right ventricular systolic pressure increased from 100 to 140 mmHg.

Both stroke index and right ventricular end-diastolic pressure were studied at rest and during exercise in 34 patients (Fig. 3). Seventeen patients showed a normal response to exercise. Their right ventricular end-diastolic pressure either stayed the same or decreased, while their stroke index showed either an increase or a slight decrease. Pulmonary regurgitation was present in only 4 of these patients. Only 2 had right ventricular systolic pressures greater than 50 mmHg.

The other 17 patients showed a major increase in right ventricular end-diastolic pressure. In 12 of these patients, stroke index either remained the same or increased. Stroke index fell in the remaining 5 patients. Pulmonary regurgitation was present in 15 of the patients in whom right ventricular end-diastolic pressure rose, and the right ventricular systolic pressure was greater than 50 mmHg in 9 of these patients. It is difficult to determine if abnormal responses to exercise were related to abnormalities of myocardial function or to the presence of residual structural abnormalities.

Discussion

Kirklin *et al.* (1965), Malm *et al.* (1966), Burnell *et al.* (1969), and Gotsman *et al.* (1969) have shown that repair of tetralogy of Fallot is feasible with a low operative mortality and excellent clinical results. Many, however, have failed to corroborate the clinical improvement with haemodynamic data. Our early experience indicated that residual abnormalities were frequently present after correction of tetralogy of Fallot. These anomalies were often observed in patients who were asymptomatic, and their presence could not have been detected without cardiac catheterisation.

In our haemodynamic studies and in those of others (Bristow *et al.*, 1962; Lillehei *et al.*, 1964; Kirklin *et al.*, 1965; Malm *et al.*, 1966; Burnell *et al.*, 1969; Gotsman *et al.*, 1969; Bristow *et al.*, 1970; Jarmakani *et al.*, 1972; Epstein *et al.*, 1973; Ruzyllo *et al.*, 1974; Finnegan *et al.*, 1976), ventricular septal defect and right ventricular outflow obstruction have been identified as the major residual abnormalities. Residual ventricular septal defect has been found in 15 to 20 per cent of patients after corrective operation. In most patients, the shunts have been small and the pulmonary/systemic flow ratios less than 2:1 (Malm *et al.*, 1966; Gotsman *et al.*, 1969). In large series of patients, the incidence of residual left-to-right shunts greater than 2:1 was 1 to 7 per cent (Malm *et al.*, 1966; Gotsman *et al.*, 1969; Ruzyllo *et al.*, 1974). The incidence of residual shunts in our study was 20 per cent. Nine per cent of our patients had a large residual defect leading to either a left-to-right shunt greater than 2:1 or a bidirectional shunt. The usual location of the residual defect was along the superior-posterior margin of the patch. The incidence of the occurrence of residual ventricular septal defect in our patients has not changed from our early to our most recent surgical experience.

Residual right ventricular outflow tract obstruction occurs often in patients after repair of tetralogy of Fallot (Kirklin *et al.*, 1965; Malm *et al.*, 1966; Shah and Kidd, 1966). Residual stenosis is considered significant when the peak right ventricular systolic pressure is greater than 80 mmHg or the right ventricular/pulmonary arterial gradient is greater than 50 mmHg. The percentage of patients with severe residual stenosis varies from zero in small series (Burnell *et al.*, 1969; Jarmakani *et al.*, 1972; Ruzyllo *et al.*, 1974) to 4 to 5 per cent in larger series (Kirklin *et al.*, 1965; Gotsman *et al.*, 1969; Ruzyllo *et al.*, 1974). Resting peak right ventricular systolic pressure was greater than 80 mmHg in 24 per cent of our patients. The most common site of outflow tract stenosis was at the level of the pulmonary annulus. No difference in the level of right ventricular systolic pressure was found between the patients with a patch across the pulmonary annulus and those without such a patch. This fact may be related to a difference in the anatomy of the right ventricular outflow tract in patients requiring a patch. The presence of a residual shunt with increased pulmonary blood flow contributes to the raised right ventricular systolic pressure in some patients.

Pulmonary regurgitation frequently occurs after the reconstruction of the right ventricular outflow tract in patients with tetralogy of Fallot. The degree of pulmonary regurgitation is difficult to evaluate, but our patients seem to have tolerated it quite well, even the 4 patients with an obstructed pulmonary artery and raised pulmonary arterial pressure. Pulmonary regurgitation was present in over half of our patients and, as expected, was associated with a widened pulmonary arterial pulse pressure. These patients frequently had high pulmonary arterial systolic pressure that may have contributed to the raised right ventricular systolic pressure.

Malm *et al.* (1966), Shah and Kidd (1966), Bristow *et al.* (1970), Epstein *et al.* (1973), and Finnegan *et al.* (1976) have shown the resting and exercise cardiac output to be normal in patients after repair of tetralogy of Fallot. Shah and Kidd (1966) showed that an increase in cardiac output with exercise is related to normal changes in heart rate and stroke volume. Bristow *et al.* (1962) reported a normal relation between oxygen consumption and cardiac output. Epstein *et al.* (1973) studied patients in an upright position doing intensive exercise. The cardiac indices of these patients were low (6·1 ± 0·3 l/min per m^2) compared with normal individuals (8·9 ± 0·3 l/min per m^2). This occurred though these patients had no residual septal defect and only minimal outflow tract gradient. In 4 of our 35 patients studied during supine exercise, the cardiac index was abnormally low in relation to oxygen consumption.

Half of our 34 patients studied showed an abnormal response to exercise. Pulmonary regurgitation was more common in the 17 patients with an abnormal response, and the right ventricular systolic pressure was more frequently raised. However, there was no significant correlation between behaviour of right ventricular end-diastolic pressure and stroke index, and the presence of residual ventricular septal defect or outflow tract obstruction. It is uncertain whether abnormal response of right ventricular end-diastolic pressure and stroke index reflects abnormal ventricular compliance or abnormal ventricular contractility. Studies of right ventricular volume would assist determination of right ventricular function. We noted, as did Bristow *et al.* (1970), that abnormalities in right ventricular function at rest were magnified during exercise, and that right ventricular end-diastolic pressure was raised to abnormal levels in several patients.

We did not routinely study left ventricular function in our patients, but intend to do so in future, since abnormalities of left ventricular function were shown in other studies. Sunderland *et al.* (1972) have shown normal left ventricular ejection fraction in children who were operated upon before the age of 2 years, but, in contrast, Jarmakani *et al.* (1972) have shown that left ventricular ejection fraction is depressed in patients operated upon at an older age. Thus, postoperative cardiac function may be dependent on the age at which operation is done.

Because of the significant incidence and severity of residual abnormalities occurring in children after tetralogy of Fallot repair, many of whom are asymptomatic, we believe that every child should undergo postoperative cardiac catheterisation. The studies should include exercise haemodynamics and assessment of left ventricular function. Understanding of the postoperative results in tetralogy of Fallot will be improved with the development of methods to measure right ventricular volume.

We wish to acknowledge the various paediatric cardiology staff and fellows who assisted and performed many of the cardiac catheterisations, and our cardiac surgeons who recognised the need for postoperative cardiac catheterisation and stressed the importance of such procedures to the parents of our patients.

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Echocardiographic study of right and left ventricular dimension and left ventricular function in patients with tetralogy of Fallot before and after surgery[1, 2]

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SUMMARY Right and left ventricular dimensions and function were determined by one-dimensional echocardiography in patients with tetralogy of Fallot before and after corrective surgery. Thirty-five children (mean age: 5·9 years) were examined; 5 of them died immediately after operation; 5 had palliative operations only. The remaining 25 had repeat echocardiography 2 to 4 and/or 8 weeks after total correction.

Compared with normal values, preoperative left ventricular dimensions were smaller than expected for body surface area (mean = 85·4% ± 1·9 SEM, range 65 to 105% of normal); 21 values were below the 5th centile. Postoperatively, left ventricular dimensions increased significantly and reached normal values in most cases (mean = 103·2 ± 2·0% SEM, range 81 to 121%). The main increase took place in the first 4 weeks ($P < 0·001$; mean difference 0·7 ± 0·14 cm). The 5 children who died after operation had smaller left ventricular dimensions than the survivors ($P < 0·01$).

Left ventricular function was evaluated by measuring mean circumferential fibre shortening, per cent shortening, and ejection fraction; they were normal in most patients and diminished only insignificantly after corrective surgery.

Right ventricular dimensions were increased preoperatively but decreased significantly ($P < 0·001$) postoperatively.

Septal movement was normal in direction and excessive in displacement in most patients before operation; immediately after operation it became flat or showed paradoxical motion. Two months after operation 50 per cent of the children showed a return to normal septal movement. Early appearance of normal septal movement could be related to the presence of significant pulmonary stenosis.

It is concluded that a high percentage of patients with tetralogy of Fallot have underdeveloped but normally functioning left ventricles which adapt well to the new postoperative state.

In previous investigations, left ventricular volume and mass were found to be diminished in patients suffering from tetralogy of Fallot, after the age of 2 years (Lev *et al.*, 1964; Lev and Eckner, 1964). Furthermore, angiographic evaluations of right and left ventricular function before and after corrective surgery showed impaired function of varying degree (Levin *et al.*, 1966; Jarmakani *et al.*, 1972; Graham *et al.*, 1971, 1976). This ventricular function even remained depressed when palliative shunt procedures preceded corrective surgery, though left ventricular and left atrial volumes and mass increased significantly after palliation (Jarmakani *et al.*, 1972; Graham *et al.*, 1976).

The aim of the present study is to investigate right ventricular and left ventricular dimensions and function using an echocardiographic technique. As left ventricular function and left ventricular volume seemed to be of greatest importance for the outcome of corrective surgery (Kirklin and Karp, 1970), we

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were particularly interested in studying left ventricular dimensions, left ventricular volume, and left ventricular function before and soon after corrective surgery, and in following the development of septal motion after surgical correction on cardiopulmonary bypass.

Subjects and methods

Thirty-five patients, 5 days to 14 years old with a mean age of 5·9 years, with tetralogy of Fallot, were examined by single beam echocardiography and cardiac catheterisation. Echocardiographic studies were performed shortly before corrective surgery and then serially 2 weeks and/or 4 weeks and/or 8 weeks after operation whenever possible. Cardiac catheterisation was performed within 24 hours of echocardiographic examination in order to confirm the diagnosis before cardiac surgery, and was repeated 2 months after surgery.

The operative technique was essentially the same for 30 patients undergoing total correction (5 of the 35 children underwent only palliative surgery and have not yet had a further operation). A standard procedure was used for surgical correction under hypothermia (down to 18°C) and aortic cross-clamping. A patch enlarging the right ventricular outflow tract was used in 20 patients.

Of the 30 patients who underwent a repair procedure, 5 died early after operation (in addition, a baby 5 days old died after palliative operation). Of the remaining 25 patients, 4 underwent a second procedure for severe residual pulmonary obstruction or for an important left-to-right shunt in the case of residual ventricular septal defect.

ECHOCARDIOGRAPHIC TECHNIQUE AND VALIDATION

Initially the echocardiograms were obtained using a Picker Echoview System 103 interfaced with an Electronics for Medicine VR6 recorder; more recently a Picker 80C ultrasonoscope and a Honeywell fibreoptic strip chart recorder were used. The electrocardiogram was simultaneously obtained for timing ventricular depolarisation; the Q wave or the beginning of the R wave was chosen for determining the time of onset of electrical systole. A 2·25 MHz transducer with an external diameter of 13 mm or a 3·6 MHz transducer of 6 mm diameter, both focused at 7 cm, were used to obtain the echocardiograms. The examination was performed in the supine position in the manner previously described by Feigenbaum (1972) and others. The mitral valve was first located, then the left ventricular posterior wall and interventricular septum were visualised simultaneously with both leaflets of the mitral valve. From this position the ultrasonic beam was directed several times medially and superiorly in order to obtain a proper and diagnostic sweep for a patient with tetralogy of Fallot (Chung *et al.*, 1973; Tajik *et al.*, 1973; Godman *et al.*, 1974; Morris *et al.*, 1975).

The pulmonary artery was searched for but could only be seen in about 50 per cent of the cases.

The echocardiographic indices studied were right and left ventricular end-systolic and end-diastolic dimensions, left ventricular volume, mean velocity of circumferential fibre shortening and shortening fraction as well as ejection fraction.

Left ventricular ejection time and pre-ejection period were measured on the aortic root echo after determination of aortic cusp opening and closure.

Left ventricular end-systolic dimension was determined along a perpendicular line at the point of closest approximation of the left ventricular endo-

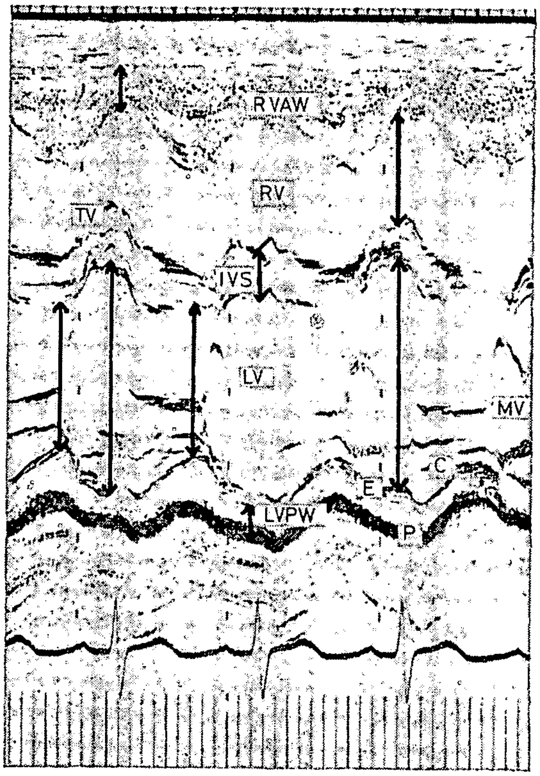


Fig. 1 *Echocardiogram of the right and the left ventricles in a 13-month-old child with severe tetralogy of Fallot. The bars indicate the different measurements that have been taken. IVS, interventricular septum; LV, left ventricle; LVPW, left ventricular posterior wall; MV, mitral valve; RV, right ventricle; RVAW, right ventricular anterior wall; E, endocard; P, pericard; C, cord.*

cardium and the left septal surface. End-diastolic dimension was measured from the left septal surface to the left ventricular endocardium at the time of onset of ventricular depolarisation as indicated by the Q or R wave of the simultaneous electrocardiogram (Fig. 1).

The right ventricular end-diastolic diameter was measured from the right ventricular endocardium to the right septal surface also at the onset of depolarisation. Care was taken to measure the end-diastolic dimension before the posterior movement of the endocardium indicating isovolumic contraction (Meyer *et al.*, 1975).

Left ventricular volumes were calculated according to the equations of Pombo *et al.* (1971), Fortuin *et al.* (1971), Teichholz *et al.* (1976), and Meyer *et al.* (1975), and compared with angiographic volume calculations using the area length method from single plane cineangiography (right anterior oblique view) and correcting for magnification and distortion (Green *et al.*, 1967).

Mean velocity of circumferential fibre shortening and percentage fibre shortening were calculated according to Karliner *et al.* (1971, 1975) using the aortic root to determine the ejection time (Paraskos *et al.*, 1971; Karliner *et al.*, 1971, 1975; Kaye *et al.*, 1975). The ejection fraction was calculated using the equation of Meyer *et al.* (1975).

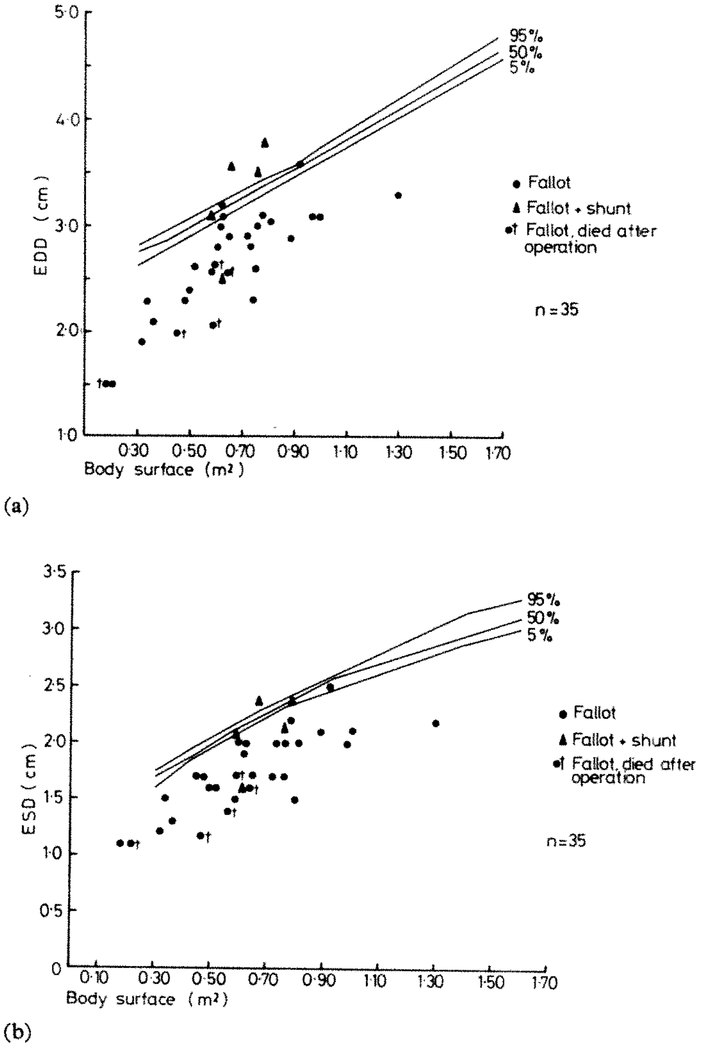


Fig. 2 *Preoperative individual end-diastolic* (a) *and end-systolic* (b) *left ventricular dimensions in comparison with the normal distribution curve as published by Epstein* et al. (*1975*) *for body surface area.*

STATISTICAL METHODS

Values are expressed as either individual values or as means ± standard errors of the mean for the number of observations given. P values of less than 0·05 are considered significant using a paired t test (preoperative samples versus postoperative samples) or using an unpaired t test (differences between groups). A linear regression equation was calculated for angiographic versus echocardiographic end-diastolic volumes (Snedecor and Cochran, 1970).

Results

(a) LEFT AND RIGHT VENTRICULAR DIMENSIONS

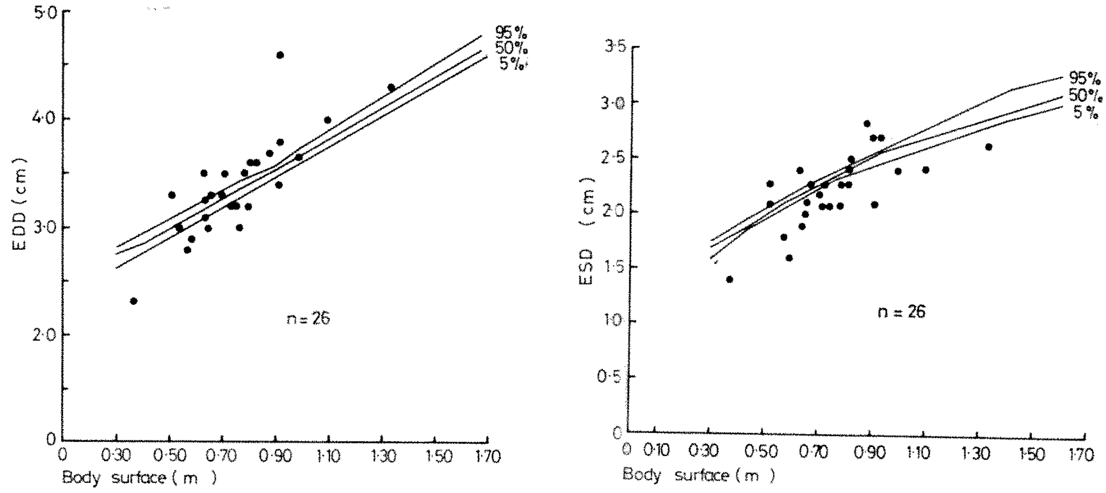
Left ventricular end-systolic and end-diastolic dimensions in our patients were related to body surface area and compared with the normal values contained in the distribution curves published by Epstein *et al.* (1975) (Fig. 2a, b). Before operation, both dimensions were much below normal; the mean value for end-diastolic dimension was 85·4 ± 1·9 per cent with a range between 65 and 105 per cent of normal; the corresponding values for end-systolic dimensions were 80 ± 2·3 per cent with a range from 52 to 101 per cent. The 5 patients who died at operation were not only small children but also had particularly small left ventricles for their body surface area. The 5 patients who had undergone a previous palliative procedure showed dimensions that approached or exceeded normal values (range 81 to 105%). Preoperative data are shown in Table 1.

Postoperatively, left ventricular diameters increased significantly and exceeded normal values in 11 cases (Table 1, Fig. 3a, b). The mean value for end-diastolic dimensions was 103·2 ± 2·0 per cent of normal with a range between 81 and 121 per cent;

Table 1

General preoperative data						*Echocardiographic measurements*							
						Preoperative				*8 weeks postoperative*			
No.	*Age*	*Sex*	*BSA* m^2	*Hb* *g/100 ml*	*Ao sat* (%)	*RVD* (*mm*)	*LVEDD* (*mm*)	*LVESD* (*mm*)	*%SID*	*RVD* (*mm*)	*LVEDD* (*mm*)	*LVESD* (*mm*)	*%SID*
1	5 days	F	0·18		54	10	15	11	26·7				
2	5 days	F	0·22	14·6	64	10	15	11	26·7				
3	3 mths	M	0·32	13·3	77	12	19	12	36·8				
4	1 yr 3 mths	F	0·36	12·4	74	17	21	13	38·1				
5	1 yr 2 mths	F	0·37	15·4	82	17	23	15	34·8	14	23	14	39·1
6	2 yr 5 mths	F	0·46	13·7	51 (spell)	16	18	12	33·3				
7	3 yr 7 mths	M	0·51	14·4	85	9	23	17	26·1	9	33	23	30·3
8	2 yr 9 mths	F	0·54	14·2	79	13	26	16	38·5	10	30	21	30·0
9	5 yr 6 mths	F	0·57	22·2	65	17	21	13	38·1				
10	5 yr 6 mths	M	0·57	19·5	60	15	31	23	26·0	21	28	18	35·7
11	4 yr	M	0·59	16·8	72	20	26	17	34·6	17	29	16	44·8
12	5 yr 5 mths	M	0·60	21·0	70	23	22	16	27·3				
13	5 yr	M	0·63	15·5	63	12	24	15	37·5	10	35	24	31·4
14	5 yr 2 mths	M	0·64	14·9	80	20	32	20	37·5	14	31	19	38·7
15	5 yr	M	0·64	15·6	83	12	26	15	42·3				
16	7 yr 9 mths	M	0·65	16·2	78	23	28	20	28·6	23	30	20	33·3
17	5 yr 11 mths	F	0·65	22·0	72	15	29	17	41·4				
18	4 yr 7 mths	M	0·65	19·4	38 (spell)	25	25	16	36·0	18	33	21	36·4
19	6 yr 10 mths	F	0·66	18·0	88	12	31	20	35·5				
20	5 yr	M	0·70	21·6	67	20	30	16	46·7	11	33	22	33·3
21	7 yr 6 mths	F	0·71	23·0	44 (spell)	10	34	24	29·4	9	35	23	34·2
22	7 yr 9 mths	M	0·74	18·6	70	31	27	20	25·9	15	32	21	31·4
23	5 yr 10 mths	F	0·74	18·8	84	15	26	15	42·3	15	32	21	31·4
24	9 yr 4 mths	F	0·77	26·8	55	22	23	15	34·7	22	30	21	30·0
25	6 yr 4 mths	M	0·79	23·4	82	19	26	17	34·6	15	35	23	34·3
26	9 yr 5 mths	F	0·80	17·4	84	21	26	16	38·5	17	32	23	28·1
27	6 yr 6 mths	M	0·81	18·9	85	20	35	21	40·0	12	36	24	33·3
28	7 yr 7 mths	M	0·82	17·8	83	16	31	22	29·0	12	36	25	30·5
29	8 yr 3 mths	M	0·88	16·8	75	18	31	20	35·5	13	37	28	24·3
30	8 yr 9 mths	M	0·91	22·6	86	14	25	14	44·0	13	34	21	38·2
31	8 yr	M	0·92	19·7	59	20	38	24	36·8	15	44	27	38·6
32	10 yr 10 mths	M	0·92	15·0	90	15	36	25	30·6	11	38	27	28·9
33	10 yr	M	0·99	15·2	74	20	28	19	32·1	20	37	24	35·1
34	12 yr	M	1·01	25·4	68	17	31	21	32·3	16	40	24	40·0
35	13 yr 10 mths	M	1·34	15·2	74	18	31	20	35·5	18	43	27	37·2

BSA, body surface area; Hb, haemoglobin; Ao sat, aortic saturation; RVD, right ventricular dimension; LVEDD, left ventricular end-diastolic dimension; LVESD, left ventricular end-systolic dimension; %SID, per cent shortening of the internal dimension.



(a) (b)

Fig. 3 *Measurements of left ventricular end-diastolic* (a) *and end-systolic* (b) *dimensions for 26 patients 2 months after successful operation, in comparison with the normal distribution curve for body surface area as published by Epstein* et al. (*1975*).

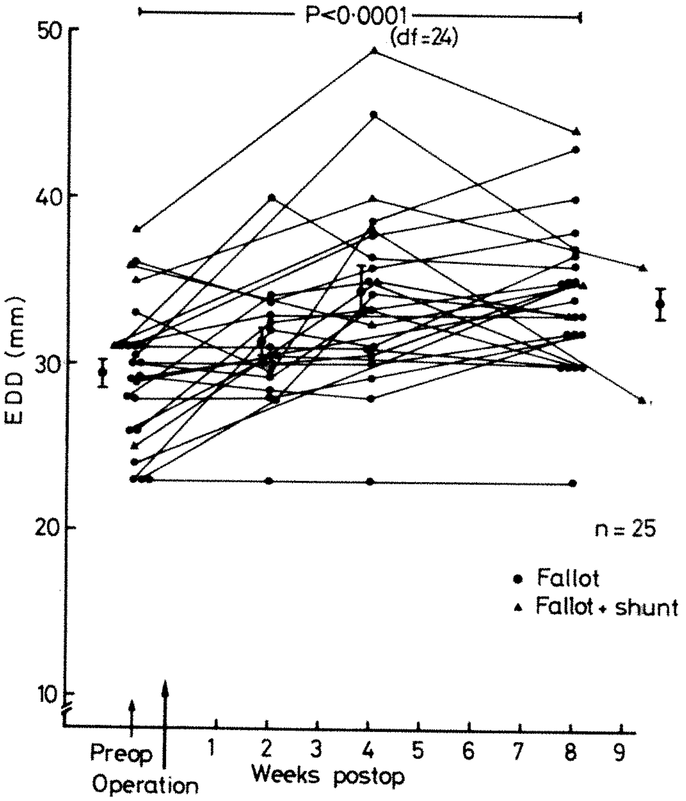


Fig. 4 *Individual sequence of left ventricular end-diastolic measurements as a function of time before and after operation. The bars indicate mean values of each group with the standard error of the mean at a given time.*

the corresponding end-systolic value was 97·3 ± 2·4 per cent, with a range from 71 to 116 per cent.

In Fig. 4, the pre- and postoperative values for end-diastolic dimensions are combined; the sequence of changes in each individual case is given as a function of time after corrective surgery. The main and most significant increase in the left ventricular diameter takes place within the first 4 weeks (the mean increase is 0·52 ± 0·15 cm, $P < 0{\cdot}001$). Between the 4th and the 8th week after surgery changes are slight and variable for individual cases; on the whole, end-diastolic dimension diminishes slightly but insignificantly.

Right ventricular end-diastolic dimensions were found to be increased preoperatively (160 ± 6·3% of normal); they diminished significantly in the two-month period after operation (the mean decrease is 0·28 ± 0·08 cm, $P < 0{\cdot}001$). In 3 patients with a significant residual pulmonary artery gradient (more than 60 mmHg) the right ventricular dimension did not diminish. Practically no change in dimension was seen in children whose values were normal before operation and in the one case who had severe pulmonary insufficiency (Fig. 5).

(b) COMPARISON WITH ANGIOGRAPHIC VOLUME CALCULATIONS

The best correlation between echo and angio techniques was found when the equation of Meyer *et al.* (1975) for calculating the volume from the echocardiogram was used, as shown in Fig. 6. The regression equation reads $y = 0{\cdot}93\,x + 4{\cdot}8$; $r = 0{\cdot}92$; $n = 41$ ($P < 0{\cdot}001$).

Before corrective surgery, echocardiographic calculations tended to underestimate left ventricular volume, while postoperatively echocardiography overestimated left ventricular volume in comparison with angiocardiographic measurements.

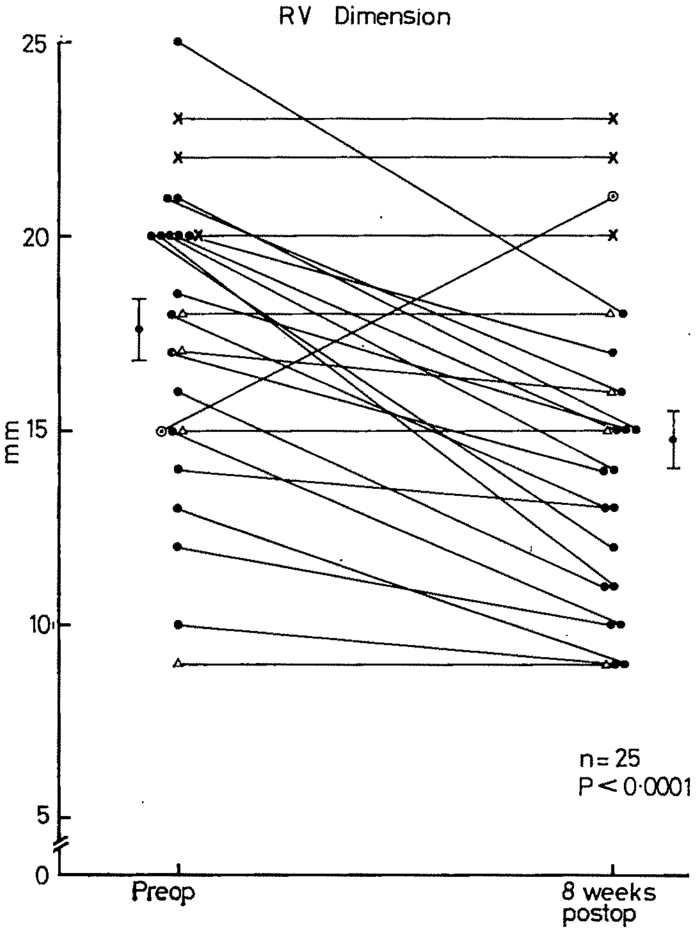


Fig. 5 *Right ventricular dimensions before operation and 8 weeks after operation. In most patients, right ventricular dimension decreased significantly* (●)*; exceptions are: patients whose right ventricular dimension was normal before surgery* (△)*, patients with conspicuous residual pulmonary stenosis* (×) *and one patient with right and left heart failure* (⊙)*, and significant pulmonary insufficiency after operation.*

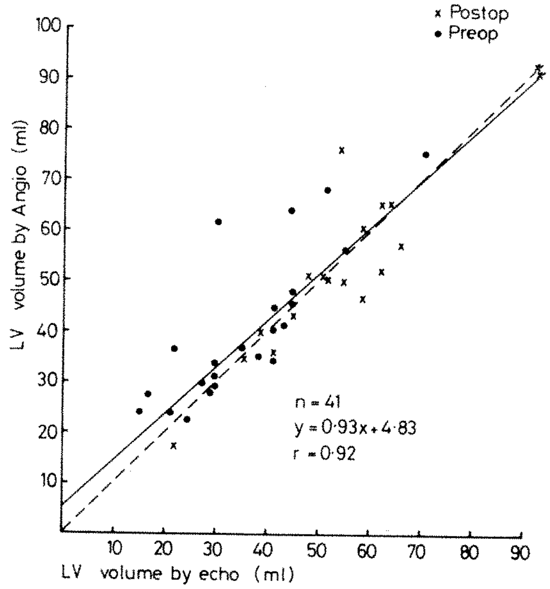


Fig. 6 *Comparison between angiographic and echocardiographic left ventricular volume calculations. The dotted line is the line of identity while the solid one is the regression line for the total group of observations (before and after operation).*

Calculated left ventricular volumes (expressed as ml/m^2) were compared before and after operation in 25 children undergoing correction for tetralogy of Fallot (Fig. 7). The mean value of left ventricular volumes was 55·6 ± 3·04 ml, with a range from 29 to 89 ml before surgical intervention. Thus left ventricular volume was abnormally small in 15 (60%) of the 25 patients and normal in only 4 children (16%).

Eight weeks after the repair procedure the left ventricular volumes had returned to normal or exceeded the normal range (mean 72·8 ± 2·3 ml/m^2 body surface area with a range of 54 to 102 ml, $P < 0{\cdot}0001$) for all except 3 patients whose volume also increased but not to normal. An abnormally large postoperative volume was found in 3 patients; it could be related to a large left-to-right shunt in 1 case (residual) and to left ventricular failure in 2, but 3 to 4 months after operation these 2 had also reached normal values.

Ten patients underwent palliative shunts; as a result of this procedure the left ventricular dimension and volume of 8 patients had returned to normal, while in 2 it remained unchanged. For the total group the mean value was 95 per cent of normal (range 60 to 120%).

(c) LEFT VENTRICULAR FUNCTION STUDIES

Ejection fraction (Fig. 8a)

Preoperatively the mean value for 35 patients was 62 ± 1 per cent with a range of 52 to 70 per cent. Six children of the total group of 35 had values below the lower limit of normal (which is 58%) (Jarmakani *et al.*, 1972). Independently of septal movement postoperatively, the ejection fraction 2 and 4 weeks after operation showed nearly identical results (mean value 64 ± 2% and 63 ± 1%, respectively). Two months after corrective surgery the mean value for a total of 25 patients had slightly but insignificantly decreased (61 ± 1% with a range of 48 to 73%).

A diminished ejection fraction was found preoperatively in 6 children; 3 of them still had abnormal values 8 weeks postoperatively. In addition, 4 children who had normal values before were found to have low values after operation. No correlation between low ejection fraction and postoperative mortality was found.

Per cent shortening fraction and mean rate of circumferential shortening (Fig. 8b, c)

Preoperatively, the shortening fraction of the internal diameter was within the normal range in 29 of 35 observations (mean value 33·8 ± 0·7%). Six patients were found to have diminished left ventricular function not only by diminished percentage of shortening fraction (below 30%, the lowest value being 26%) but also by ejection fraction as described previously.

Two and 4 weeks after operation the percentage shortening fraction increased significantly (37·5 ± 1·7%). This increase could have been the result of digitalisation which formed part of the postoperative treatment. Nevertheless, 3 of 17 and 3 of 21 patients, respectively, showed a reduced contractility, with values below or at 30 per cent. Eight weeks after operation 22 of 25 successfully operated children had normal values (mean value 34·1 ± 0·9%) and 3 had borderline shortening of the internal diameter (30%); the mean value differed only insignificantly from those obtained preoperatively.

Mean rate of circumferential fibre shortening

The mean rate of circumferential shortening was also evaluated before and after operation. All the values calculated were found to be above 1·04 circ/s (the lower limit of normal) in the preoperative group (Cooper *et al.*, 1972; Kaye *et al.*, 1975; Tynan *et al.*, 1975). Those patients who had diminished ejection fractions and diminished or borderline per cent shortening of internal diameter, were found

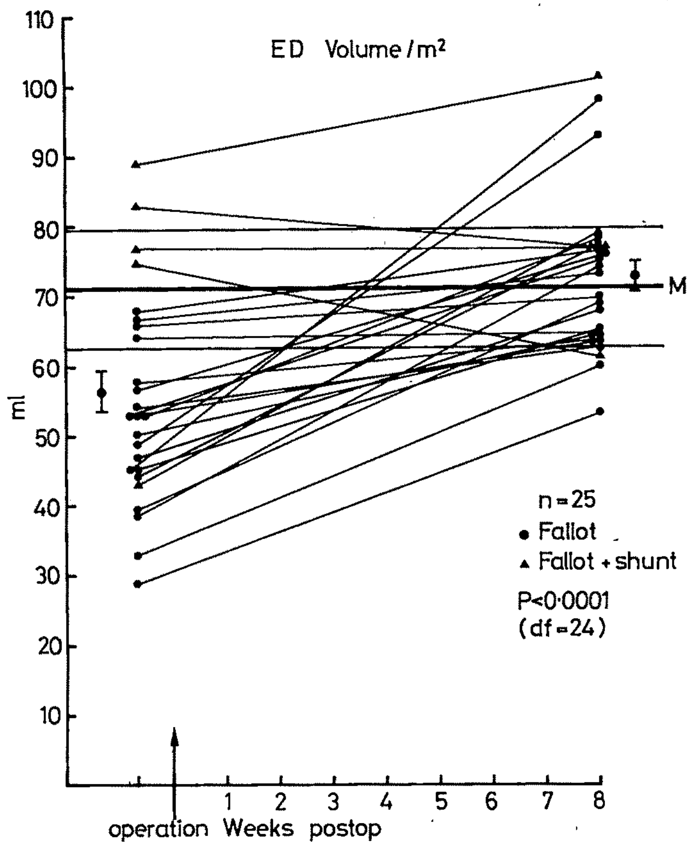


Fig. 7 *Comparison of our left ventricular end-diastolic volume indices (/m²) determined before and after operation by echocardiography with the normal values, mean, and standard deviations (horizontal lines), as published by Graham's group (1971). The vertical bars indicate pre- and postoperative mean values and the standard error of the mean.*

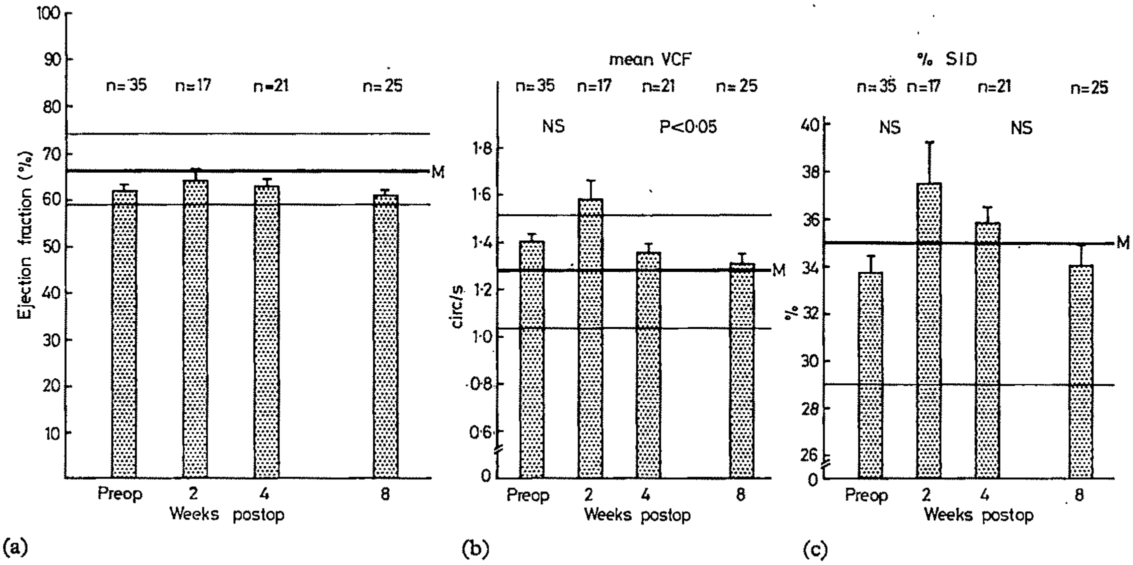


Fig. 8 *Left ventricular function indices as a function of time before and after operation. The horizontal lines indicate normal mean values and the standard deviations. The columns indicate our mean values with the standard error of the mean. Mean VCF, mean velocity circumferential fibre shortening; % SID, per cent shortening of internal diameter.*

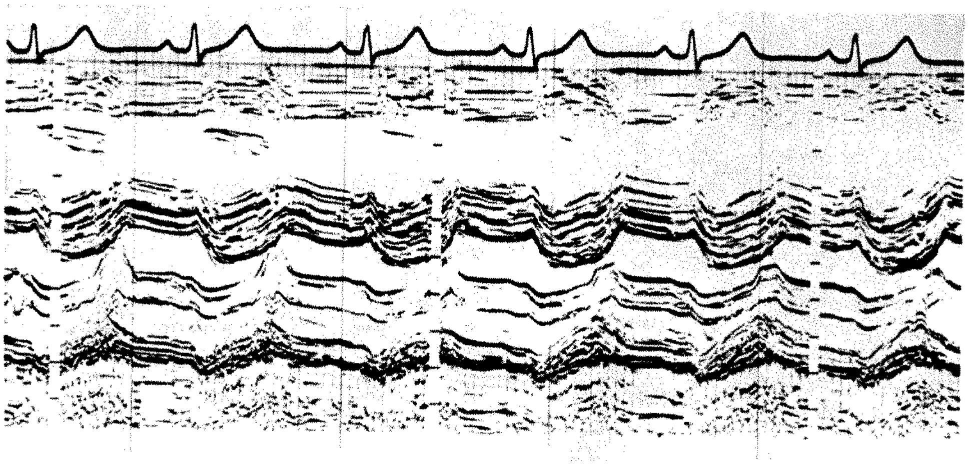


Fig. 9(a)

Fig. 9 *Different types of septal movement seen after operation.* (a) *Normal but excessive septal movement;* (b) *abnormal flat movement* (*type B*)*;* (c) *abnormal movement with double posterior movement during ventricular systole and diastole;* (d) *abnormal paradoxical movement.*

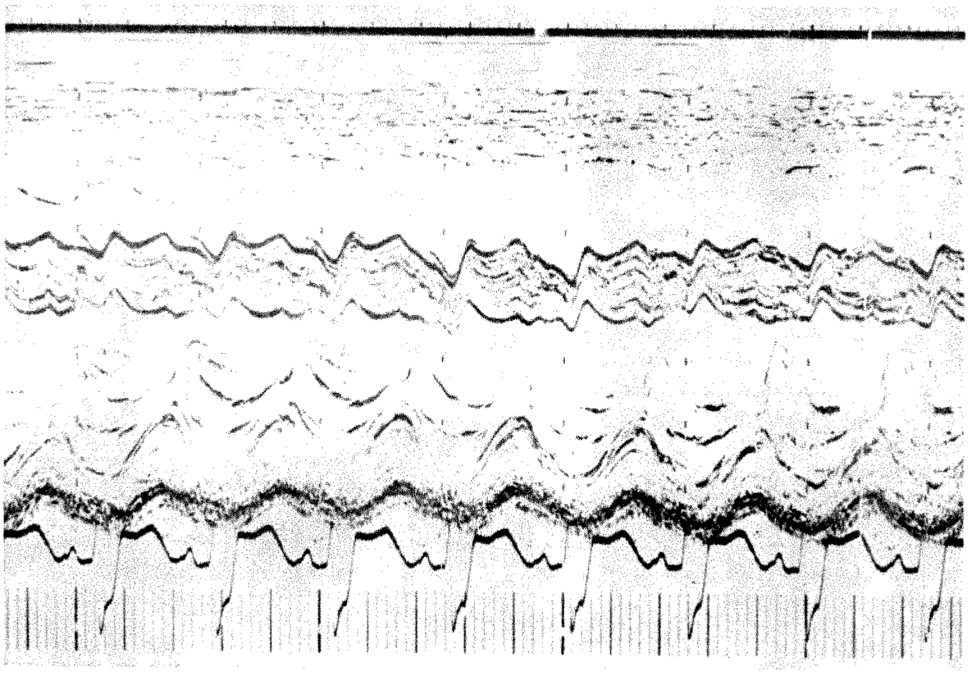


Fig. 9(b)

to have low normal mean circumferential fibre shortening rates (1·05 to 1·15). Immediately after operation mean circumferential fibre shortening rate increased and exceeded the upper limit of normal. Statistically this increase was not significant; when the total groups were compared, it was however

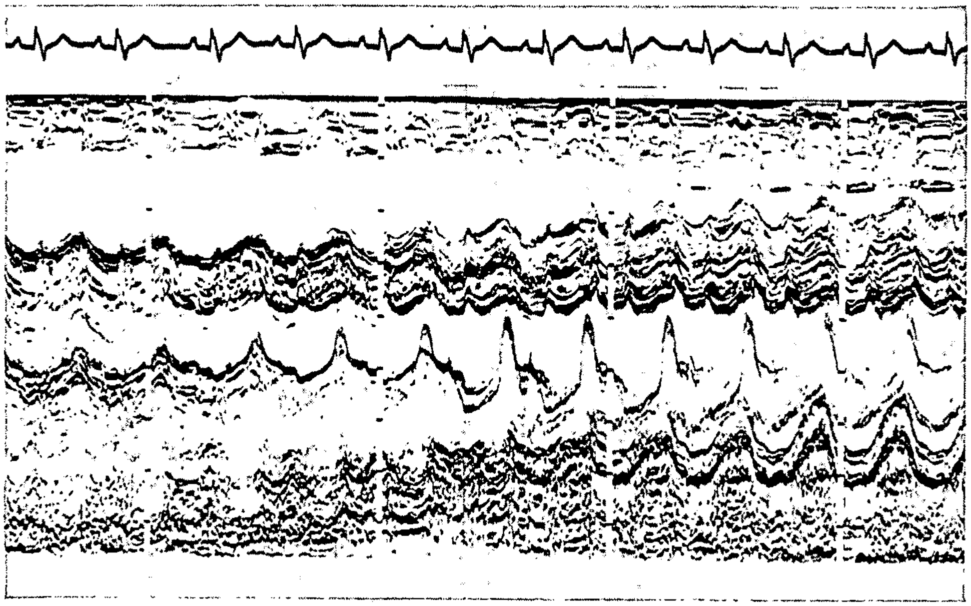


Fig. 9(c)

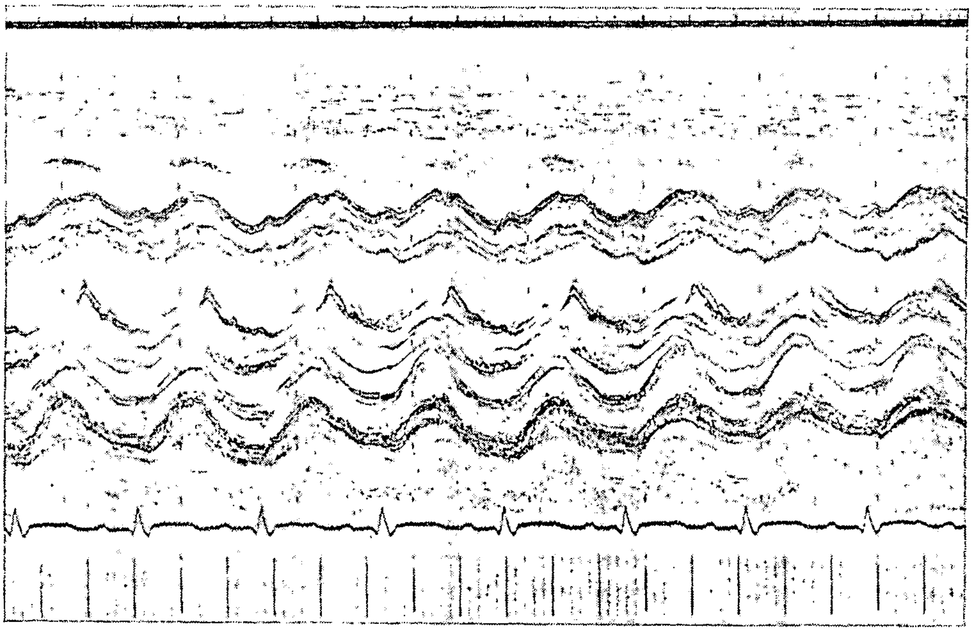


Fig. 9(d)

significant in 17 patients studied longitudinally before and after operation (paired t test, $P < 0{\cdot}025$).

Eight weeks after operation the mean value decreased to 1·32 ± 0·04 circ/s. One of 25 patients had an abnormally low value of 0·95 circ/s and 6 more were again in the lower range (below 1·15).

SEPTAL MOVEMENT

Before surgical correction, septal movement was found to be normal in direction but frequently

Table 2 *Types of septal movement as a function of time (before and after operation)*

Septal movement	*Pre-operatively (N = 35)*	*2 weeks post-operatively (N = 17)*	*4 weeks post-operatively (N = 21)*	*8 weeks post-operatively (N = 26)*
Normal	95%	31%	38%	50%
Flat (type B)	6%	50%	38%	19%
Paradoxical	3%	19%	24%	31%

excessive in displacement in 32 of the 35 patients; 3 children had abnormal septal movement (Table 2; Fig. 9a, b, c, d). Early after operation (2 weeks) it became flat in 50 per cent and paradoxical in 19 per cent but remained normal in 31 per cent. All patients with a persistently normal motion except one were found to have a residual gradient of more than 30 mmHg across the pulmonary valve (range 35 to 65 mmHg) at postoperative cardiac catheterisation (2 months after operation). The one child who had no pulmonary stenosis yet normal motion had an important residual left-to-right shunt at ventricular level. Those patients with a persistent flat or paradoxical movement 2 months after operation had pulmonary gradients ranging from 10 to 35 mmHg only.

With increasing time after operation the percentage of normal but also of paradoxical movement increased while the flat movement was less frequently encountered (Table 2).

Discussion

(A) METHODS

Left ventricular volumes estimated from the echocardiographic dimension of the left ventricle have been shown to correlate well with the volumes calculated from biplane but also from single plane cineangiograms in both adults and children (Feigenbaum, 1972; Kaye *et al.*, 1975; Teichholz *et al.*, 1976). The volume calculation is based on the assumption that the long axis of the left ventricle equals twice the minor axis. As it had become evident that this assumption was not always correct, different empirical equations were derived during the past years (Fortuin *et al.*, 1971; Meyer *et al.*, 1975; Teichholz *et al.*, 1976).

In order to find out which of these equations would fit best for tetralogy of Fallot patients, we compared volumes calculated according to the formulae of Feigenbaum, of Fortuin, of Teichholz, and of Meyer with our angiographically determined values before and after corrective surgery. The best correlation was found when our echocardiographic values were calculated by means of Meyer's equation as shown in Fig. 6 ($r = 0{\cdot}92$ for 41 compared values, $P < 0{\cdot}001$). In spite of this good correlation considerable deviations were found in some cases. A variety of factors may be responsible for differences of volumes calculated from angiograms and echocardiograms.

Firstly, the measurements were not made simultaneously but within 24 hours in somewhat different conditions. Thus sedation of the patients during cardiac catheterisation as well as differences in heart rate are likely to change the haemodynamic situation.

Secondly, in tetralogy of Fallot before operation, variations in the degree of infundibular stenosis can influence left ventricular preload. Such changes can contribute to the differences in observations in any one method, but also certainly to the differences between two methods.

Finally, the administration of propranolol (for anoxic spells) may induce changes within a few hours. Postoperatively, septal motion abnormalities could be the reason for some important differences in angiographic and echocardiographic volume calculations.

It must also be considered that any small error made in determining left ventricular dimensions is magnified when the volume is calculated because the measurements have to be cubed. Though the results of these calculations are useful in order to observe trends of changes in longitudinal studies, we tend to put more emphasis on left ventricular dimensions and changes in dimension and less on absolute values and volume calculations. However, even measurements of dimensions are not without problems (Popp *et al.*, 1975).

Percentage shortening and velocity of circumferential fibre shortening of the internal diameter have been shown to correlate better with measurements obtained angiographically than volumes both in adults and infants (Cooper *et al.*, 1972; Karliner *et al.*, 1975; Kaye *et al.*, 1975). These indices seem to be less influenced by assumptions regarding left ventricular geometry. In a comparison study between mean circumferential fibre shortening rate derived from single plane angio- and echocardiograms, Kaye *et al.* (1975) demonstrated a good correlation and showed that mean circumferential fibre shortening rate was the more sensitive index. It is known, however, that these indices are also influenced by a number of variables including fibre length at rest (preload), ventricular systolic pressure (afterload), chamber shape, and heart rate. Increased afterload diminishes mean circumferential fibre shortening rate, while certain drugs (digoxin) increase it (Karliner *et al.*, 1975). Care must, therefore, be taken in the interpretation of results, whether obtained by angiographic or echocardiographic techniques.

(B) RESULTS

A decreased left ventricular end-diastolic volume has been reported in patients with tetralogy of Fallot both in cineangiographic studies and anatomical specimens (Lev *et al.*, 1964; Jarmakani *et al.*, 1972). This 'hypoplasia' of the left ventricle was specially evident when the patients' age exceeded 2 years. Our data confirm this underdevelopment of left ventricular size (as shown in Fig. 2a, b and Fig. 7). Contrary to the study by Jarmakani, no clear correlation was found between preoperative left ventricular end-diastolic dimension and haemoglobin or haematocrit.

From our data it appears that the young children with severe left ventricular hypoplasia have a higher operative mortality though several were successfully operated on with left ventricular diameters of only 65 per cent of normal. This seems to favour a palliative procedure before total correction in patients with small left ventricles. In our study 5 patients with small left ventricular dimensions did have shunt procedures followed by total correction. Though none of them died, 3 of them had stormy postoperative courses with prolonged left ventricular failure. We are, therefore, not convinced that small left ventricular volumes are an indication for palliation rather than corrective surgery (Graham *et al.*, 1976). The causes of the left ventricular underdevelopment in tetralogy of Fallot patients are not well known.

One could speculate that the stenosed pulmonary outflow tract together with the malaligned aorta favours flow from the right ventricle to the ascending aorta during fetal development, upsetting the balance between right and left ventricular output. This is in fact unlikely to cause left ventricular underdevelopment because most of the left ventricular filling in the fetus occurs from the inferior vena cava through the foramen ovale and not through the pulmonary veins. After birth, when left ventricular output depends essentially on pulmonary blood flow, the decreased pulmonary blood flow occurring in tetralogy of Fallot patients diminishes pulmonary venous return as well as left atrial and left ventricular filling. One would thus expect a progressive increase in relative left ventricular hypoplasia with increasing age of the patients. So far we have not been able to show this in our study. Indeed the regression line for left ventricular dimension versus body surface area in patients with tetralogy is not significantly different from the normal regression line. After corrective surgery the left ventricular dimension increases. This increase is relatively slow and insignificant up to 2 weeks after operation but 4 weeks after the operation it becomes highly significant ($P < 0{\cdot}001$). Between 4 and 8 weeks after operation there are only small changes, the general tendency being a levelling off.

The right ventricular dimension which was large preoperatively in most of our patients decreased and approached normal values whether or not an outflow patch was used at surgery. Right ventricular dimension did not decrease in the presence of a moderate or severe outflow tract obstruction or in haemodynamically significant pulmonary incompetence. As we did not investigate right ventricular function indices, a comparison with the results obtained by Graham's group (1976) cannot be made.

The different indices used for left ventricular function followed a similar pattern of change before and after operation. Abnormal function is suggested in only a small percentage of patients (17%) by abnormalities of 2 if not all 3 indices. Such inadequate left ventricular function has been recognised previously in angiographic studies by Graham's group (1971, 1976). Its cause is as yet unknown, but abnormal myocardial metabolism from hypoxia with myocardial fibrosis as a consequence could be responsible (Friedli *et al.*, 1977).

By 2 weeks after corrective surgery all 3 indices of left ventricular function increased temporarily; this increase was insignificant except for per cent SID. It could be explained either by an increase in preload, a change in heart rate, or the effect of treatment with digoxin and diuretics (Karliner *et al.*, 1975). Further investigations in the earliest postoperative phase will be necessary to understand this effect. Four and 8 weeks after operation all values decreased but remained on the mean in the normal range.

Because abnormal septal movement could bias calculations of left ventricular function indices, a comparison of pre- and postoperative values was made for patients with normal septal motion only. The same trends are observed as for the total group (Fig. 10). The fact that mean circumferential fibre shortening rate is within normal limits even in cases with abnormal ejection fraction and per cent SID makes us wonder whether the lower limits of normal should be put at a value of 1·15 or even 1·2.

It must be emphasised that with single beam echocardiography only a small area of the septum and of the ventricular posterior wall can be studied; thus there remains the possibility that dyskinetic areas are missed (Kaye *et al.*, 1975; Teichholz *et al.*, 1976). Considering the whole of our observations we can confirm that some patients with tetralogy of Fallot have diminished or impaired left ventricular

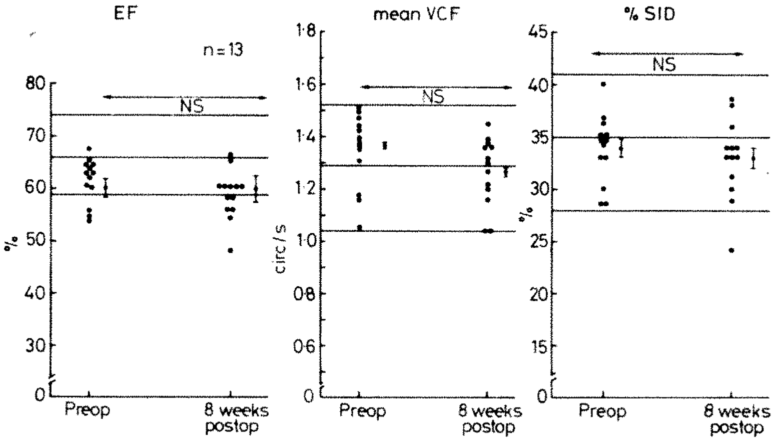


Fig. 10 *Left ventricular function indices for patients with normal septal motion only (N = 13) before operation and 8 weeks after operation. The horizontal lines indicate the distribution of the normal values (mean ± standard deviation). The bars show the mean values ± the standard error of the mean. There are no significant differences between the groups for either index. EF, ejection fraction; mean VCF, mean velocity circumferential fibre shortening; % SID, per cent shortening of internal diameter.*

function pre- and postoperatively. However, most children show normal function indices, whether there is abnormal septal motion or not. Certainly the abnormalities observed in our patients were less important and less frequent than those reported by Jarmakani *et al.* (1972).

Septal movement

Abnormal septal movement immediately after extracorporeal circulation for repair of intracardiac defects has been observed previously. The abnormal motion decreases with time after operation and in most but not all cases returns eventually to normal. The cause of this abnormal movement is still unknown but seems to be multifactorial (Righetti *et al.*, 1977).

In tetralogy of Fallot, the interventricular septum is directly affected by the operative procedure as a Teflon patch is used for closure of the ventricular septal defect. This can cause septal injury, which in some cases may result in persistent abnormalities in septal motion. Nevertheless, after a relatively short time (9 weeks), 50 per cent of the operated cases returned to normal septal motion. At that time another 31 per cent still showed paradoxical and 19 per cent persistently flat motion.

In the presence of a complete bundle-branch block with left anterior hemiblock paradoxical movement is known to persist; 2 of our patients have abnormal septal motion probably related to this cause (Assad-Morell *et al.*, 1974). Another patient had a large perioperative myocardial infarction which can be held responsible for the abnormal movement even 18 months after operation. For the 5 remaining patients with paradoxical and the 5 patients with flat motion we do not have an explanation; time will tell whether they will finally return to normal. Though an open or absent pericardium can be the cause of septal movement abnormalities, we do not believe that this is the main cause in our cases since 50 per cent of the patients have returned to normal excursion by 8 weeks after the procedure. But it could explain the early postoperative observation of increased anterior movement of the entire heart during systole from absence of restraint (Payvandi and Kerber, 1976).

Finally, one would expect right ventricular volume overload in the case of significant pulmonary insufficiency to be a cause of persistence of abnormal motion. This may have played a role in 3 of our patients, the only ones with haemodynamically significant pulmonary insufficiency. In these, septal motion remained paradoxical in 1 case and flat in 2. It cannot be held responsible for abnormal septal motion in the other cases. Indeed the fact that right ventricular dimension decreased in nearly every case is an argument against significant volume overload in our series.

The most striking observation concerning septal movement was the fact that 31 per cent of the operated children showed normal but excessive septal motion 2 weeks after surgery. When these patients were evaluated by cardiac catheterisation all but one were found to have a residual pulmonary gradient of more than 30 mmHg and in 3 cases even of above 60 mmHg. Therefore we believe that early appearance of normal but excessive septal movement should be considered indicative of a persistent pulmonary stenosis in patients who had a repair procedure for tetralogy of Fallot.

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Echocardiographic features of secondary left ventricular hypertrophy

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SUMMARY Echocardiograms showing left ventricular cavity and mitral valve were recorded and digitised in 100 patients with secondary left ventricular hypertrophy caused by severe hypertension (23), aortic valve stenosis (21), fixed subaortic stenosis (13), and postoperative aortic stenosis (13), or regurgitation (30). Left ventricular dimension and its rate of change were determined and related to mitral valve opening. These values were compared with those from 30 patients with hypertrophic cardiomyopathy. In the patients with secondary left ventricular hypertrophy, cavity size and peak circumferential fibre shortening rate were normal. In diastole, the peak rate of increase of dimension was reduced in 56, and mitral valve opening, normally synchronous with minimum dimension, was delayed in 78, both the result of abnormal left ventricular relaxation. The septal to posterior wall thickness ratio was greater than 1·3 in 40. Values for delay in mitral valve opening were distributed bimodally in the population of patients with secondary left ventricular hypertrophy, with one subgroup in which it was normal and the other in which it was significantly delayed. The distribution of the latter, along with those of values of peak rate of dimension increase and septal to posterior wall thickness ratio were indistinguishable from those in the patients with hypertrophic cardiomyopathy. Abnormalities similar to those of hypertrophic cardiomyopathy therefore occur in patients with secondary left ventricular hypertrophy, and these echocardiographic criteria cannot separate the two conditions.

Diastolic abnormalities are prominent in hypertrophic cardiomyopathy. Left ventricular end-diastolic pressure may be raised, and disturbances in the timing of wall motion be present, with delayed mitral valve opening, reduced peak rate of dimension increase, prolonged rapid filling period, and evidence of incoordinate relaxation (Sanderson *et al.*, 1978; St John Sutton *et al.*, 1978). Secondary left ventricular hypertrophy, by contrast, has been described as a homeostatic and basically beneficial process (Linzbach, 1960; Goodwin, 1974) in which an increase in wall thickness and mass occur to normalise peak systolic wall stress. It thus appears to be qualitatively different from hypertrophic cardiomyopathy, and it has been suggested that the two can be separated by measurements of the relative thickness of the septum with respect to that of the posterior left ventricular wall (Henry *et al.*, 1973). The purpose of the present study was to investigate the relation between the two processes in greater detail, with particular reference to diastolic events. It was hoped that further criteria for their distinction might become apparent on the basis of such observations and that these might also be of value in the investigation of those relatively uncommon cases in which the two processes appear to coexist.

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Methods

Echocardiograms of 100 patients with secondary left ventricular hypertrophy were studied, and diagnoses are given in Table 1. Those with systemic hypertension all had resting diastolic blood pressures above 120 mmHg before the start of treatment. The severity of the outflow tract obstruction was severe enough to require operation in all the patients with aortic or fixed subaortic stenosis. None had

Table 1 *Clinical material*

Secondary left ventricular hypertrophy:		100
Severe hypertension	23	
Aortic valve stenosis	21	
Fixed subaortic stenosis	13	
Postoperative:		
Aortic stenosis	13	
Aortic reflux	30	
Hypertrophic cardiomyopathy		30

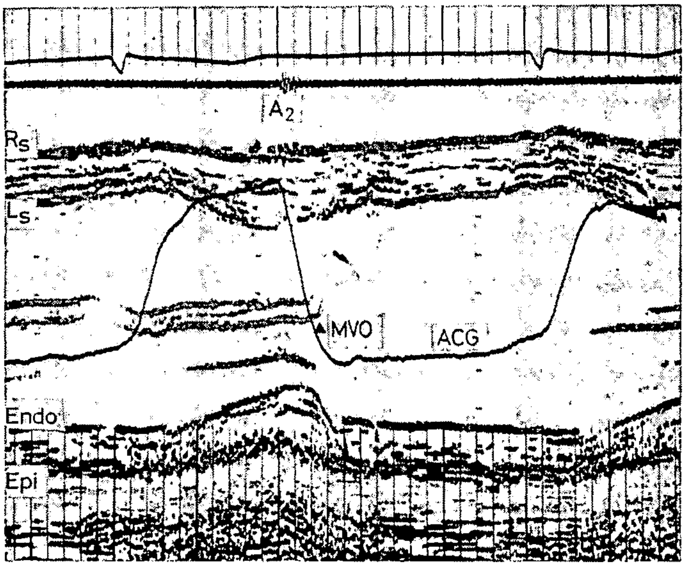

Fig. 1 *Echocardiogram from a patient with hypertension, showing right (Rs) and left (Ls) sides of the septum, endo- and epicardial surfaces of the posterior wall, recorded with an apex cardiogram (ACG), and phonocardiogram showing aortic valve closure (A2). The timing of mitral valve opening (MVO) is shown.*

significant aortic regurgitation or mitral valve disease. All the patients studied had echocardiographic evidence of left ventricular hypertrophy in that septal or posterior wall thickness, or both, were greater than 12 mm, the upper limit of normal. Results from these patients were compared with those from the echocardiograms of 30 patients with classical hypertrophic cardiomyopathy, diagnosed on angiographic criteria (Steiner, 1964).

Echocardiograms were recorded as previously described (Fig. 1) (Gibson and Brown, 1973), with the patient in the left lateral position using a Smith-Kline Ekoline 20 ultrasonoscope and a Cambridge Instruments photographic recorder, operating at a paper speed of 100 mm/s. Echocardiograms were recorded at the level of the tips of the mitral valve cusps, so that the time of mitral valve opening could be detected as that of initial separation at the start of diastole. The definition of the posterior wall was increased using the switch gain technique, and by a modification of the swept gain to produce a reverse ramp.

Echocardiograms were digitised as previously described (Gibson and Brown, 1973) using a Summagraphics digitiser and a Prime 300 computer system. From these records, the following measurements were made (Fig. 2).

(1) End-diastolic and end-systolic cavity size, wall thickness, and septal thickness. End-diastolic events were taken as simultaneous with the onset of the Q wave of the electrocardiogram, and end-systolic as those simultaneous with minimum cavity dimension.

(2) Peak normalised rate of reduction of dimension during systole (VCF), expressed in s^{-1}.

(3) Peak rate of increase of dimension during diastole.

(4) Early diastolic filling period, as defined in Gibson and Brown (1973).

(5) The time interval between minimum cavity dimension and the onset of mitral valve opening, and the increase in dimension occurring during this time expressed as a percentage of the total increase.

Mean values for each of the 5 groups of patients with secondary left ventricular hypertrophy were derived, and compared with normal, and also with those from the patients with hypertrophic cardiomyopathy. In addition, the distribution of variables was plotted as a histogram from all the patients with secondary hypertrophy taken together so that mean values and distributions could be compared with similar plots of the population with hypertrophic cardiomyopathy. Departures of these samples from normal frequency distributions were investigated using the Kolmogorov-Smirnov test. For normally distributed samples, standard deviations were calculated, and the significance of differences between means checked by t tests.

Results

(1) LEFT VENTRICULAR DIMENSIONS

The results for individual groups of patients with secondary left ventricular hypertrophy are given in Table 2, where they are compared with those from normal subjects and patients with hypertrophic

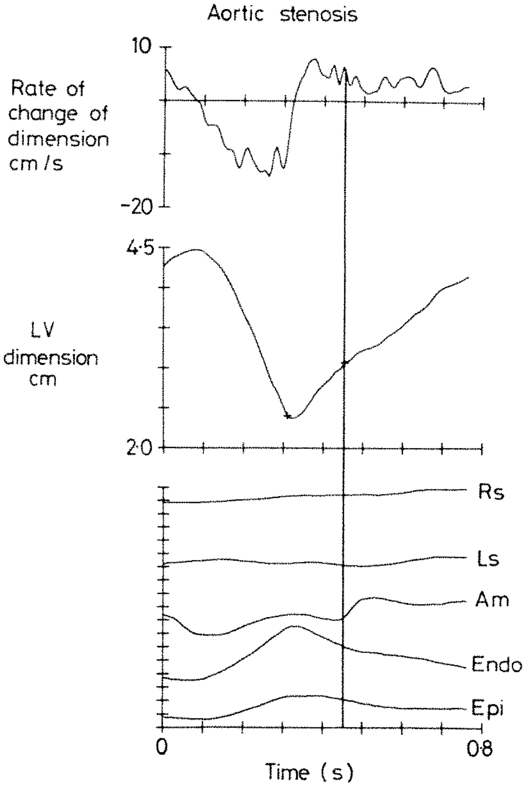

Fig. 2 *Digitised echocardiogram from a patient with aortic stenosis, showing, from below, original data, and above, left ventricular dimension and (top) rate of change of dimension. The cross represents the timing of A2, and the vertical line that of MVO, which is delayed with respect to minimum dimension. The peak rate of increase of dimension is reduced below 10 cm/s, and early diastolic filling period is prolonged.*

cardiomyopathy. End-diastolic dimensions did not differ from normal in any of the groups, and end-systolic dimension was normal in all patients except those with hypertrophic cardiomyopathy, where it was reduced ($P < 0·01$). Posterior wall and septal thickness were greater than normal in all patients, by definition, but were significantly less than those recorded in hypertrophic cardiomyopathy. In general, the ratio of septal to posterior wall thickness was greater than 1·3:1 in patients with hypertrophic cardiomyopathy, but this was not always the case (Fig. 3). Values greater than 1·3:1 occurred in nearly half those with secondary left ventricular hypertrophy, where they were distributed as a single normal frequency curve (Fig. 3). A figure for the ratio of septal to posterior wall thickness of 1·3:1, or indeed any other value did not separate patients with secondary left ventricular hypertrophy from those with hypertrophic cardiomyopathy.

(2) SYSTOLIC WALL MOVEMENT

Systolic rates of wall movement, assessed in terms of peak VCF were normal in all the groups of patients with secondary left ventricular hypertrophy, but somewhat greater than normal in those with hypertrophic cardiomyopathy ($P < 0·05$). This difference was no longer apparent when peak rates of wall movement were expressed in absolute (cm/s) rather than normalised (s^{-1}) units, and so was probably a reflection merely of the reduced end-systolic cavity size.

(3) DIASTOLIC EVENTS

The mean value of peak rate of dimension increase was reduced significantly below normal in all groups of patients with secondary left ventricular hypertrophy, and the distribution of values throughout the whole population of these patients is shown in Fig. 4, where it is compared with that of the patients with hypertrophic cardiomyopathy. Mean values and standard deviations were not significantly different. Significant prolongation of early diastolic filling period occurred in patients with secondary

Table 2 *Echocardiographic data*

	Normal	*Hyper-tension*	*Aortic stenosis*	*Subaortic stenosis*	*Postoperative*		*Hypertrophic cardiomyopathy*
					AS	*AR*	
End-diastolic dimension (cm)	4·7 ± 0·32	4·6 ± 1·0	4·9 ± 1·0	4·1 ± 1·1	4·8 ± 1·2	4·9 ± 1·0	4·7 ± 0·3
End-systolic dimension (cm)	2·9 ± 0·35	3·0 ± 1·0	3·3 ± 0·9	2·5 ± 1·1	3·2 ± 0·8	3·5 ± 1·0	2·4 ± 0·3
Peak VCF (s^{-1})	2·4 ± 0·3	2·3 ± 0·9	2·5 ± 1·0	2·5 ± 1·1	2·2 ± 1·0	2·0 ± 0·9	3·2 ± 1·0
Posterior wall thickness (cm)	0·85 ± 0·2	1·2 ± 0·3	1·2 ± 0·3	0·9 ± 0·3	1·1 ± 0·3	0·9 ± 0·3	1·4 ± 0·4
Septal thickness (cm)	0·90 ± 0·1	1·5 ± 0·7	1·5 ± 0·2	1·3 ± 0·6	1·7 ± 0·7	1·5 ± 0·3	2·2 ± 0·5
Septal/PW thickness ratio	1·1 ± 0·1	1·4 ± 0·5	1·3 ± 0·4	1·5 ± 0·5	1·5 ± 0·6	1·8 ± 0·8	1·7 ± 0·6
Peak rate of dimension increase (cm/s)	18 ± 3	10 ± 1	12 ± 5	12 ± 4	11 ± 4	12 ± 6	13 ± 6
Delay in mitral valve opening (ms)	3 ± 5	70	50	25	60	60	75
Outward movement before mitral valve opening (%)	0 ± 2	16	11	7	18	25	28

Mean ± 1 standard deviation, of normally distributed populations.

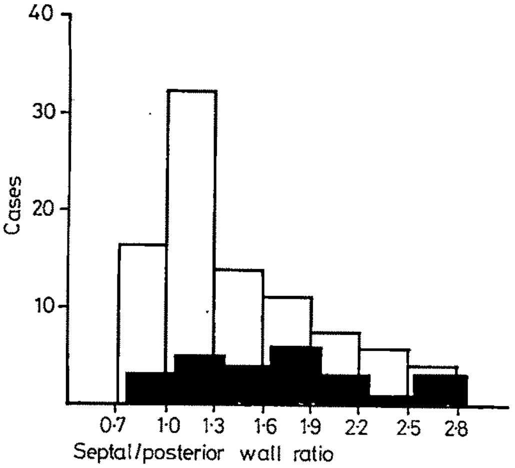

Fig. 3 *Histograms showing the distribution of values of septal/posterior wall ratio. Open columns represent the patients with secondary left ventricular hypertrophy, and solid ones, those with hypertrophic cardiomyopathy. The latter have been displaced slightly to the right for clarity.*

left ventricular hypertrophy as well as in those with hypertrophic cardiomyopathy (Table 2). The distribution of the delay in the onset of mitral valve opening with respect to minimum cavity dimension is shown in Fig. 5. For patients with secondary left ventricular hypertrophy, this distribution is bimodal ($P < 0{\cdot}001$, with respect to normal distribution). This departure is because approximately 40 per cent of the patients with secondary left ventricular hypertrophy have mitral valve opening at the normal time, while in the remainder it is delayed. This latter subgroup showed a distribution indistinguishable from that occurring in patients with hypertrophic cardiomyopathy. During the period between minimum dimension and mitral valve opening, an abnormal increase in dimension occurred in all groups of patients with secondary left ventricular hypertrophy, particularly those after aortic valve replacement, as well as in those with hypertrophic cardiomyopathy (Table 2). Thus secondary left ventricular hypertrophy could not be distinguished from hypertrophic cardiomyopathy on the basis of these diastolic events.

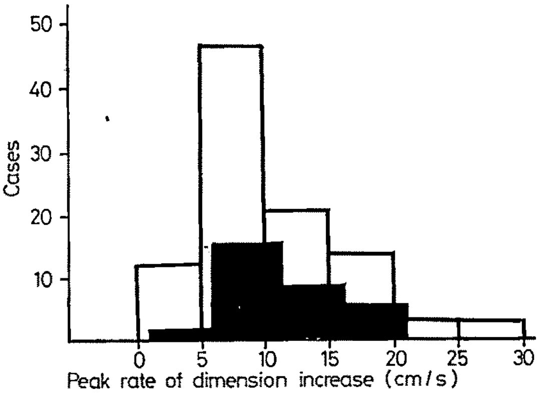

Fig. 4 *Histograms showing distribution of values of peak rate of dimension increase. Layout as in Fig. 3.*

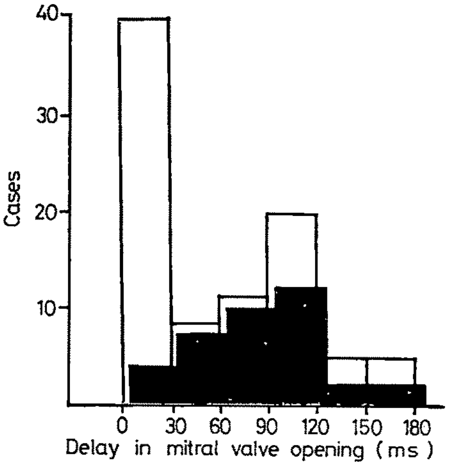

Fig. 5 *Histograms showing distribution of values of the delay in mitral valve opening. Layout as in Fig. 3.*

Discussion

The present study has shown similarities between the echocardiographic features of secondary left ventricular hypertrophy and those of hypertrophic cardiomyopathy. Differences of degree do exist, however; left ventricular cavity size was smaller at end-systole, and the extent of hypertrophy was greater in cases with hypertrophic cardiomyopathy, though this difference is readily explicable on the basis of clinical selection, since in patients with valvular heart disease, symptoms were not necessarily the result of the hypertrophy itself. It was not possible to achieve any useful separation of the two conditions using the ratio of septal to posterior wall thickness. It has previously been suggested that values of this ratio greater than 1·3 are pathognomonic of hypertrophic cardiomyopathy (Henry *et al.*, 1973), but more recently, this view has been questioned (Bulkley, 1977). Not only does the ratio of septal to posterior wall thickness give no indication of the degree of hypertrophy, but normal values have been recorded in hypertrophic cardiomyopathy

(Rossen *et al.*, 1974), and abnormal ones in normal infants (Larter *et al.*, 1976), weight lifters (Menapace *et al.*, 1977) and other sportsmen, patients with right ventricular hypertrophy (Goodman *et al.*, 1974), and those with reduced posterior wall thickness caused by myocardial infarction. The present results indicate that it cannot be used to distinguish secondary left ventricular hypertrophy from hypertrophic cardiomyopathy. In particular, values greater than 1·3 cannot be taken as diagnostic of additional cardiomyopathy in the presence of a condition capable of causing left ventricular hypertrophy.

Systolic rate of wall movement, assessed in terms of peak VCF, was normal in our patients with secondary left ventricular hypertrophy. This finding confirms previous observations of mean VCF, and is compatible with the idea that hypertrophy is a homeostatic process to normalise wall stress (Hood *et al.*, 1968; Grossman *et al.*, 1975). Left ventricular diastolic properties, however, were clearly abnormal in all groups of patients with secondary left ventricular hypertrophy. Previous studies of diastole in such patients have concentrated on the static pressure-volume characteristics of the cavity or have attempted to assess the material properties of the wall in terms of stress-strain relations (Mirsky, 1976). The present observations show that dynamic aspects of left ventricular filling are also very abnormal in these patients. Peak rate of dimension increase was reduced below the 95 per cent confidence limit of normal in over half, and the period of early diastolic filling was prolonged in a manner exactly resembling that occurring in mitral stenosis. The distribution of these abnormalities was indistinguishable from that in the group of patients with hypertrophic cardiomyopathy (Sanderson *et al.*, 1978; St John Sutton *et al.*, 1978). Since mechanical obstruction to left ventricular inflow is most unlikely in patients with secondary left ventricular hypertrophy, this pattern of diastolic wall movement is likely to be caused by abnormal relaxation. Though its mechanism is clearly different from mitral stenosis, its effects on left ventricular filling are the same, the degree of interference being inversely related to the filling period, and thus worse when heart rate is high.

A third diastolic abnormality, also seen in hypertrophic cardiomyopathy, was delay in mitral valve opening with respect to the timing of minimum dimension. This differed from the two previous ones in that values were not normally distributed in the population of patients studied. In less than half, the timing of mitral valve opening was essentially normal, whereas in the remainder it was delayed by a median value of approximately 90 ms, and this latter group appeared to have a distribution almost identical with that of hypertrophic cardiomyopathy. In part, this delay appears to represent yet another manifestation of abnormal relaxation, but its bimodal distribution, in comparison with the unimodal one describing values of the peak rate of dimension increase, suggests that additional factors are involved. Significant dimension increase occurs in these patients before mitral valve opening, indicating that a change in cavity shape occurs during isovolumic relaxation. It seems likely, therefore, that this additional factor is a degree of incoordinate relaxation. Evidence for this has been presented from analysis of angiocardiograms (Sanderson *et al.*, 1977) and echocardiograms (Sanderson *et al.*, 1978; St John Sutton *et al.*, 1978) of patients with hypertrophic cardiomyopathy. In addition, delayed mitral valve opening is also common in patients with ischaemic heart disease and segmental contraction abnormalities (Upton *et al.*, 1976), and angiographic studies suggest that in this condition also, it is evidence of asynchronous relaxation in different regions of the cavity. We conclude, therefore, that relaxation is commonly abnormal in patients with secondary left ventricular hypertrophy, not only with respect to its rate, but also to its degree of co-ordination in different regions of the cavity.

The present results may have implications in the assessment of the diastolic properties of the left ventricle, either in terms of pressure-volume relations or those between wall stress and strain. Attempts to describe the material properties in terms of simple elastic or viscoelastic models have hitherto assumed that these properties remain constant throughout the period of diastole studied. In patients with left ventricular hypertrophy, relaxation appears to be prolonged and frequently incoordinate throughout rapid filling, so that myocardial properties cannot be assumed to be constant during this time. Except in late diastole, therefore, these simple models are likely to be inappropriate.

Secondary left ventricular hypertrophy thus appears to be a more complex condition than is frequently suggested. Peak rates of wall movement are normal during systole, and on this basis it might be said that left ventricular 'function' is unimpaired. However, it is as much a function of the left ventricle to fill as to eject, and the characteristics of filling in these patients are very abnormal. These abnormalities of timing are quite distinct from those of static pressure-volume or stress-strain relations, and are such as to become progressively more significant as heart rate increases. They can be detected non-invasively using the techniques that we have described, and any assessment of overall left ventricular function in such patients seems incomplete without knowledge of their presence or absence.

The computing equipment used in this study was provided by the DHSS as part of its experimental programme.

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Analysis of left ventricular behaviour in diastole by means of finite element method

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SUMMARY The human left ventricle in diastole can be modelled as a passive structure with incremental internal pressure change being considered as the load. Recent developments in engineering stress analysis provide techniques for predicting the behaviour of structures with complex geometry and material properties, as is the case with the left ventricle. That which is most appropriate is the finite element method which requires the use of a large digital computer. The ventricles of 2 patients have been studied during diastole, the geometries having been derived from cineangiographic data (biplane), and the pressure by means of catheter-tip manometers. Various descriptions of myocardial stress/strain relations have been assumed and applied to the left ventricular wall in order to obtain the best match between the calculated and observed deformation patterns. The manner in which the value and distribution of stiffness in the left ventricle influences the shape change can therefore be determined, and possible clinical implications deduced.

It is generally accepted that abnormalities of ventricular filling may influence overall cardiac function. In the presence of left ventricular hypertrophy, pressure-volume relations are abnormal, and peak rates of diastolic wall movement reduced. Coronary artery disease may cause abnormal wall movement during isovolumic relaxation caused by asynchronous relaxation so that at the time of mitral valve opening, myocardium in non-ischaemic areas may be at or near its end-diastolic position. In order to use these observations of cavity size and configuration to predict the mechanical behaviour of the myocardium, it is necessary to consider relations between wall stress and strain (displacement). Initial attempts to do this were based on the assumption of linear elasticity and unrealistic geometrical models such as spheres or ellipsoids. Since the ventricle is a three-dimensional object with no special planes of symmetry, profiles in at least two planes are needed at each instant, most satisfactorily provided, at present, by biplane angiography. Pressure is reliably measured by a catheter tip manometer, and estimates of wall thickness can be made by echocardiography or cineangiography. If myocardial properties are to be assessed in this way, a comprehensive description must include values for the three-dimensional stress for all regions of the wall. The longitudinal and circumferential stresses may vary across the wall between endo- and epicardium, and also in different parts of the ventricle, particularly when its shape is irregular, while shear stresses are also present in the wall. Further, the myocardium itself is not homogeneous, and it has also been known for over three hundred years to have a spiral structure. In addition, the properties of myocardium cannot be described in simple terms. It is probably not linearly elastic, may show viscous effects, and values are dependent on the direction in which they are measured. Simple estimates, based on Laplace's law and ellipsoidal models do not take account of these considerations, so that their possible clinical importance has not been assessed. In order to circumvent these difficulties, we have used the finite element technique. The essence of this is that a continuous solid which is acted on by forces or deformations is idealised into an assemblage of separate finite regions or elements. These are taken to be interconnected at specific points (nodes) on their common boundaries. Assuming a relation between stress and strain within each element, a set of equations can be derived relating nodal forces to nodal displacements. The number of these equations is large, and depends on the fineness of subdivision chosen for the actual solid, the choice being limited

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by the capacity of the computer and computing time which is available. The technique thus allows the interrelations between wall stresses, wall position, and material properties to be investigated. Its use to calculate wall stress requires a detailed knowledge of the material properties of myocardium, which is not at present available. In the present study two cases have been investigated in detail. The method used was to compare observed wall displacement during diastole with that predicted by the finite element method. These predictions depend on the mechanical properties of the wall specified in the modelling procedure, so that the extent to which their alteration affected left ventricular pressure-volume relations, and in particular the agreement between observed and predicted values of wall displacement could be quantified. In this way, it was hoped to get some idea of the possible significance of factors such as the properties of the mitral annulus, the effects of variation in shear modulus or regional myocardial properties or the implication of the fibrous structure of the wall, which cannot be studied using the standard Laplace approach, and yet which may have clinical significance.

Methods

Two patients were studied in detail. Case 1 had anginal pain, but normal left ventriculogram and coronary arteriograms. Case 2 had a dilated left ventricular cavity, but normal coronary arteriograms, and was assumed to have cardiomyopathy. Haemodynamic results are given in Table 1.

Left ventriculography was performed in postero-anterior and lateral projections at 50 frames/s, with a No. 8 Millar catheter with a micromanometer at its tip. Left ventricular pressure was recorded throughout the angiogram photographically, at a paper speed of 200 mm/s. Cavity outlines and wall thickness were digitised frame by frame as previously described (Gibson and Brown, 1975).

From these biplane films, a three-dimensional reconstruction of the left ventricle was made. Two templates were constructed for each of the views chosen for analysis, which corresponded with the time of minimum left ventricular pressure. These profiles were then transferred to a block of polyurethane, at right angles to one another. The block was then painted, and the corners gradually removed until only 2 lines of paint remained, corresponding to the two biplane outlines. Though this technique clearly contains a subjective element, the resulting models appeared to resemble left ventricular cavity shape, and it was of interest that the septal region was clearly apparent, though not obvious on either of the original cavity outlines. Using these models as templates of the cavity, wall thickness was built up around them using plaster of Paris, to a depth indicated by the wall thickness measurements from the angiograms around the base of the heart, decreasing at the apex to a thickness of 2 mm. The grid for the finite element model was then inscribed by hand, and the three-dimensional co-ordinates of the nodal points measured using a Ferranti 'Conquest' 3D digitiser.[1]

Table 1 *Haemodynamic values*

	Case 1	*Case 2*
Right atrial pressure (mmHg)	$\overline{3}$	$\overline{19}$
Right ventricular pressure (mmHg)	25/0,5	57/10,19
Pulmonary artery pressure (mmHg)	25/10 $\overline{(13)}$	55/23 $\overline{(30)}$
Left ventricular pressure (mmHg)	120/5,10	130/12,25
Cardiac index (l/min per m^2)	3·6	3·0
Ejection fraction (%)	68	45

FINITE ELEMENT MODEL

Thirty-six brick type finite elements were chosen to represent the left ventricle, consisting of 6 layers and 6 elements per layer. The top layer, 1 mm thick, was used to describe the annulus fibrosus, and the bottom layer, 10 mm in diameter and 2 mm thick, to describe the apex (Keith, 1907). The model is illustrated in Fig. 1 and described in detail elsewhere (Yettram and Vinson, 1978a). It was considered to be restrained only in the region of the atria, i.e. along the upper, inner, edge of the annulus fibrosus. Pressure loads were defined from the diastolic pressure record, and were assumed to be uniform throughout the ventricle. Regional variation in pressure has been shown in man (Traill *et al.*, 1978), though only during early diastole. Right ventricular and pericardial pressures were not considered.

The elements of the assemblage were given various combinations of elastic properties reviewed in detail elsewhere (Yettram and Vinson, 1978b). A specimen set of these properties is given in Table 2. Here the annulus was considered to be isotropic, whereas the myocardium was taken as having a longitudinal stiffness one-half that in the circumferential or cross wall direction. The apex was taken as having properties of collagen. The computer programme used to solve the equations has been described in detail elsewhere (Vinson, 1977), and was run on the University of London CDC computer system and on the Prime 300 system at Brompton Hospital.

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[1] By courtesy of RAE, Farnborough.

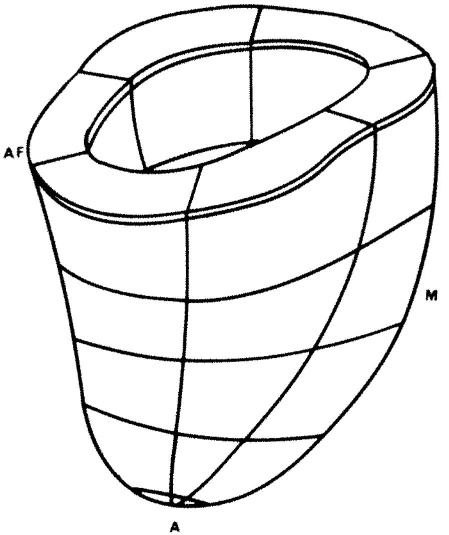

Fig. 1 *Finite element idealisation of left ventricle. M: myocardium, AF: annulus fibrosus, A: apex.*

Table 2 *Specimen set of elastic properties—myocardium*

E_x	8	G_{xy}	5·41	μ_{xy}	0·24	μ_{yx}	0·48
E_y	16	G_{yz}	5·41	μ_{yz}	0·48	μ_{zy}	0·48
E_z	16	G_{zx}	5·41	μ_{zx}	0·48	μ_{xz}	0·24

E: modulus of elasticity (kN/m²); G: modulus of rigidity (kN/m²); μ: Poisson's ratio. Material principal directions denoted by x, y, z.

PARAMETRIC STUDIES OF LEFT VENTRICULAR BEHAVIOUR

A number of modifications was then made to the left ventricular wall properties, and the relation between observed and predicted noted. These modifications included:

(1) Alterations in the properties of the annulus fibrosus. This was initially assumed to be a ring of collagenous tissue, with elastic properties as defined in Table 3. Subsequently, it was remodelled as having elasticity similar to that of myocardium.

(2) The apex was initially assumed to consist of fibrous tissue, with a diameter of 1 cm, and so to have properties similar to those of collagen. Comparison was also made with the apex having elasticity varying between that of the myocardium and that for collagen.

(3) Non-homogeneous myocardium. Following a suggestion of Nikravesh (1976), the ventricle was remodelled as being stiffer toward the base than the apex. The values were then reversed, so that the ventricle was stiffer at the apex.

(4) Cross-wall stiffness. Based on the suggestion of Janz and Grimm (1972) the transverse or cross-wall elasticity in the outer two-thirds of the ventricular wall might be one-half the tangential value. Thus the myocardium in case 1 was modified to have a tangential stiffness of twice that of the transverse stiffness. Shear modulus is an independent variable and was taken as being unaffected by this manoeuvre.

Table 3 *Initial elastic properties—annulus fibrosus*

E_x	$3·9 \times 10^5$	G_{xy}	$1·573 \times 10^5$	μ_{xy}	0·24	μ_{yx}	0·24
E_y		G_{yz}		μ_{yz}		μ_{zy}	
E_z		G_{zx}		μ_{zx}		μ_{xz}	

E: modulus of elasticity (kN/m²); G: modulus of rigidity (kN/m²); μ: Poisson's ratio.

(5) Shear modulus. Shear modulus was then studied, and was reduced from an initial value of 5·41 kN/m² to 4 and finally 1·52 kN/m², the last value being that suggested by Janz and Grimm (1972).

(6) The ratio of longitudinal to circumferential stiffness. This value was reduced to 0·91 derived from earlier work using ellipsoidal models (Yettram and Vinson, 1978b), from its initial value of 1. The effects of a further reduction to 0·5 were also studied.

(7) Effects of fibre angle. Since fibre angle varies across the wall from +60° to −60°, its effects could not be investigated in detail using the present model with wall thickness represented by only a single element. Nevertheless, if the inner third of the wall is more flexible than the remainder (Janz and Grimm, 1972), then there may well be a net effective spiral angle away from the circumferential direction. Accordingly, arrangements were examined of spirals at 10° and 30°, clockwise, from base to apex.

(8) Effects of myocardial infarction. Initially, an infarction may be modelled as a region more extensible than surrounding myocardium, but over 2 to 4 weeks it becomes replaced by fibrous tissue. Accordingly, both types were modelled, each involving 20 to 30 per cent of the total myocardial volume (Parmley *et al.*, 1973). Three sites were chosen, shown in Fig. 2. These included the basal and apical halves of the free wall, and an anteriorly positioned vertical strip.

Throughout all the above analyses, values for wall stress were also derived. Using the generalised three-dimensional approach, there were 6 stresses to be considered at any point. These are the 3 direct and 3 shear stresses; more easily interpretable are the maximum principal stress, and the local hydrostatic stress.

Results

When the left ventricular wall is assumed to have the mechanical properties given in Table 2, then the

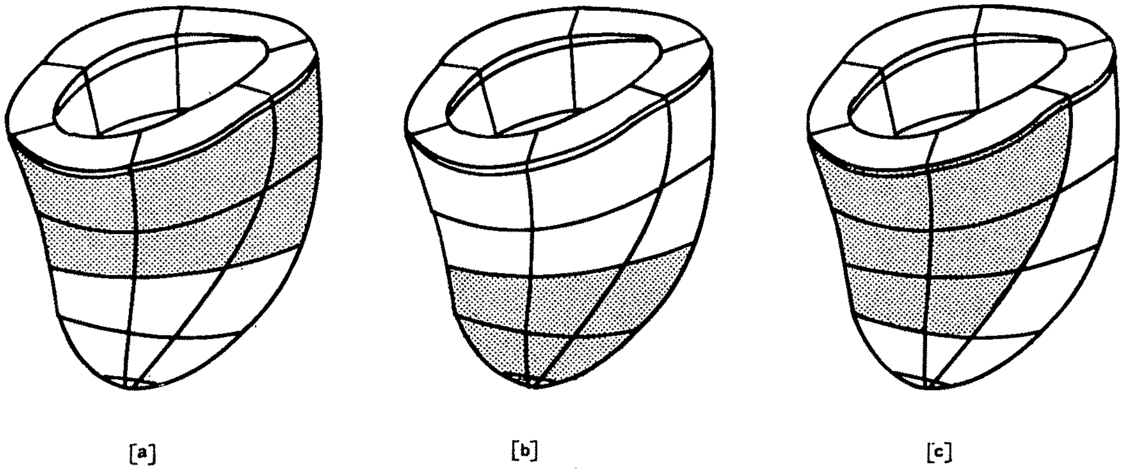

Fig. 2 *Three infarcted regions considered.* (a) *upper infarct,* (b) *lower infarct,* (c) *anterior infarct.*

deflection profiles which result are shown in Fig. 3. These are based on the displacements of the nodal points on those mid-plane sections representing the PA and lateral views. These are compared with the observed outlines of the cavity on the two angiograms. In comparing the two, allowance must be made for the fact that the angiogram does not present a true section but rather an overall profile in any particular projection, so that regions distant from the plotted region may deflect enough to form the boundary as seen on the x-ray silhouette. The distributions of the maximum principal stresses/unit internal pressure on the endo- and epicardial surfaces are shown in Fig. 4. The highest values seen in the cases examined appeared to be over the right anterior and left posterior regions of the endo-

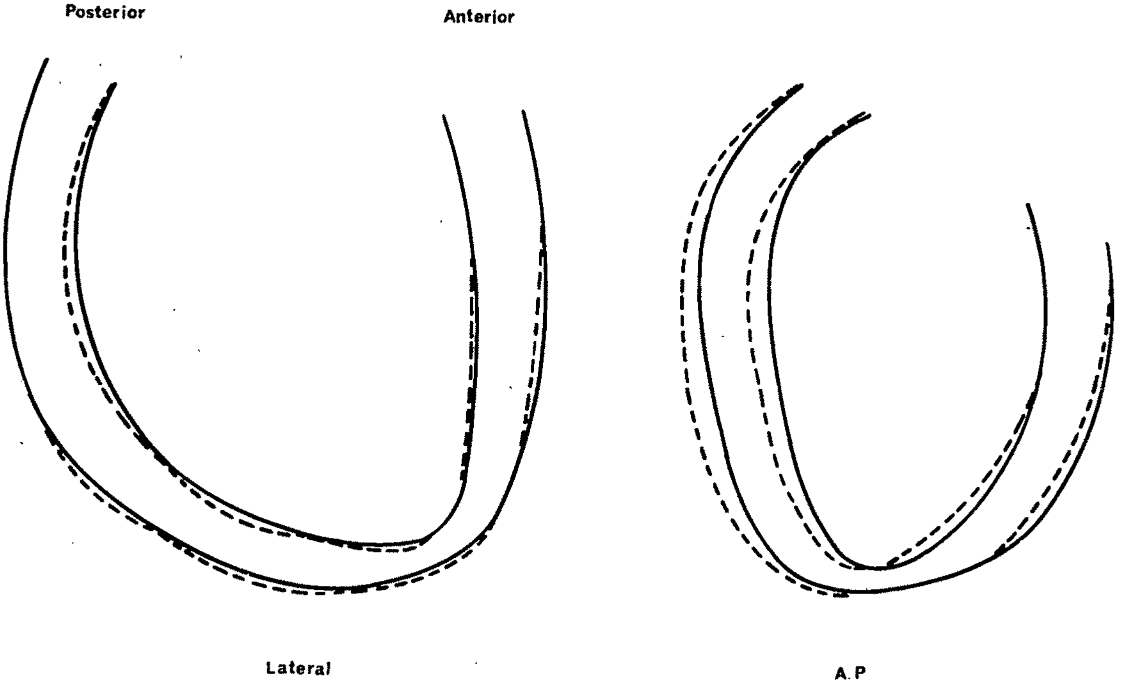

Fig. 3 *Deflection profiles for myocardium (shown as dashed line) under increment of internal pressure (case 2).*

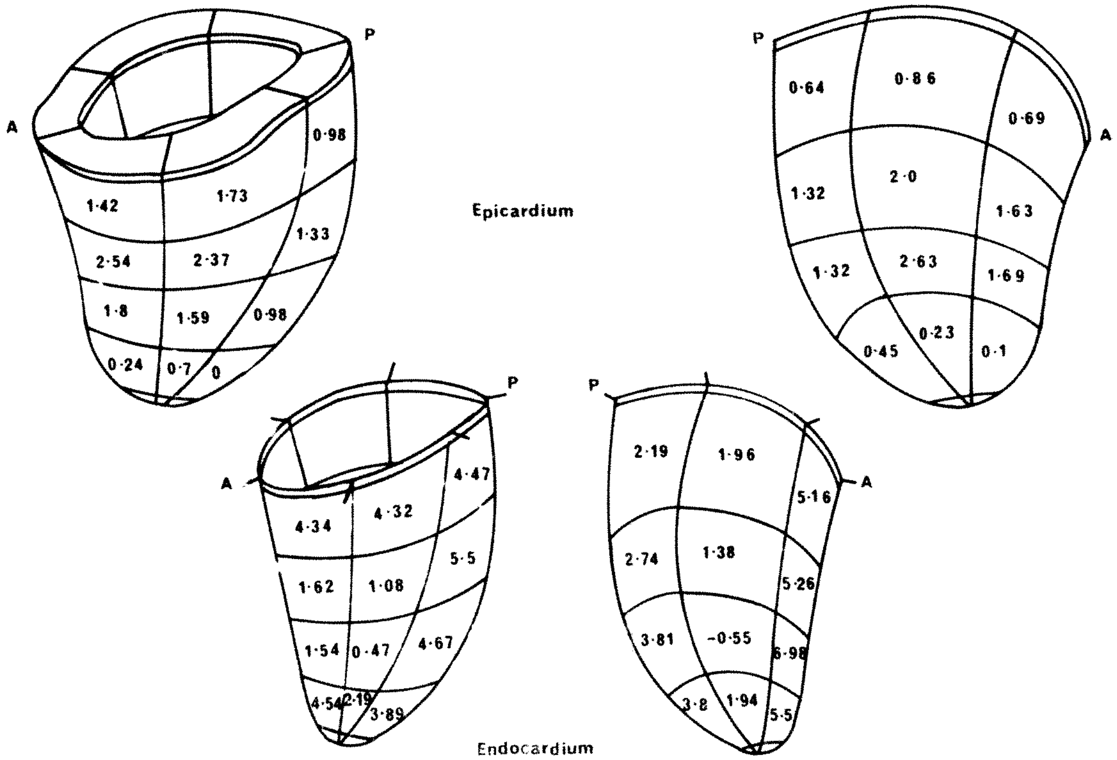

Fig. 4 *Patterns of absolute values of principal direct stresses per unit internal pressure over epicardial and endocardial surfaces (case 2).*

cardium. These values are of the same order as those obtained by Hamid and Ghista (1974), though these authors observed maximum values towards the apex.

ANNULUS FIBROSUS

Initially the annulus fibrosus was given the mechanical properties of collagen. When it was remodelled to have the same properties as myocardium, this resulted in improved agreement between observed and predicted values for displacements, in that overall movement of the cavity towards the septum occurs, instead of relative akinesis under the previous conditions. With a completely rigid mitral valve ring, whose outer edge is constrained not to move upwards, the overall increase in volume is less than with a flexible ring, thus rendering the ventricle stiffer.

APEX

When the stiffness of the apex was altered there was no change in the pattern of wall movement. The properties of the apex, therefore, do not appear critical in determining the pattern of wall movement during diastole.

MYOCARDIAL PROPERTIES

In the previous sections, the properties of the myocardium have been assumed to be uniform throughout the left ventricle. It was noted however, in case 1, that inward movement was observed towards the apex, which did not seem compatible with any passive model. When the ventricle was remodelled to give non-homogeneous myocardial properties from base to apex in an effort to explain this, agreement between observed and predicted displacements became less good in both cases. When the base was considered to be stiff, then the amplitude of movement was too great at the apex. In case 1, the ventricle was then remodelled as being stiffer at the apex, but this resulted in deflections that were too large, both in terms of regional wall movement and of overall volume increase. Modification of cross-wall stiffness had little effect on predicted displacements, but a reduction in shear modulus from 5·41 to 4·0 kN/m^2 caused a pronounced increase in the posteroanterior deflections. A further reduction to 1·52 kN/m^2, as suggested by Janz and Grimm (1972), again increased the overall deflection in the posteroanterior, with a lesser effect in the lateral. When the ratio of longitudinal to circumferential stiffness was altered from 1·0 to 0·91, deflections were unaltered. However further reduction to 0·5 produced results that compared well with the angio deflection showing appropriate regional movement though the overall effect was still slightly too great. The high sensitivity to this ratio that has been previously reported by studying ellipsoids (Yettram and Vinson, 1978b) appears to be merely a function of the use of simplistic models, which disappears when a more realistic approach is used. Predicted displacements, however, were very sensitive to the two changes in effective fibre angle of 10° and 30°. A spiral structure effectively makes the wall less stiff, and significant displacements now appear in the lateral view. The model used therefore suggests that the ratio of circumferential to longitudinal modulus, the variation in fibre angle, and to a lesser extent in shear modulus are important factors in determining displacement during diastole, while the properties of the apex are not. Agreement was not improved by the assumption of regional differences in material properties.

EFFECTS OF MYOCARDIAL INFARCTION

When the infarction was taken as flexible, with elasticity one-quarter that of the surrounding myocardium, the main effect was local distension, particularly when the infarct involved the basal part of the ventricle. When the infarct was given the properties of collagen, the effects were more complex. The infarcted area appeared rigid, as expected, but in addition the whole ventricle appeared stiffer, particularly when the basal region was involved. This effect was not a generalised one, but was the result of reduced local movement, both at the site of the infarct itself, and also on the opposite wall, in this case, the septum.

Discussion

There is a considerable body of evidence to suggest that the physical properties of the myocardium are abnormal in left ventricular hypertrophy or coronary artery disease (Mirsky, 1976). Methods have been suggested whereby the material properties of the left ventricular wall, in terms of its elasticity, can be derived from measurements of cavity size, wall thickness, and diastolic pressure. In order to use those methods, based on Laplace's law, however, a number of simplifying assumptions about cavity shape and the nature of the myocardium itself must be made. In the present study we have used the technique of finite element analysis in order to circumvent some of these limitations. Once this more versatile technique is introduced, it immediately becomes apparent that comprehensive estimates of deformation and wall stress require a corresponding knowledge of the material properties of the myocardium. This includes specific information about the apex and mitral annulus, variation in elastic modulus across the wall or in different regions of the cavity, knowledge about shear moduli and fibre angle, and finally consideration of the fibrous structure of the myocardium itself. This information is not necessary when using the Laplace equation, and thus has been little considered in the past.

Finite element methods have been used by a number of authors using a variety of element types. Most previous analyses have assumed the left ventricle to have either a circular or an elliptical cross-section. Gould *et al.* (1972) used a convenient longitudinal axis passing through the apex of the left ventricular angio, the left and right sides of the chamber were revolved about this axis, and these analysed using shell ring elements. Janz and Grimm (1972) assume the diastolic ventricle to have a circular cross-section and use a ring element for their analysis. Janz *et al.* (1974) refined this analysis to accommodate non-linear geometric effects. Neckyfarow and Perlman (1976) also assume a circular cross-section but use a thick shell hexahedron. The three-dimensional brick type element was employed by Hamid and Ghista (1974), but they used single plane angio data and assumed an elliptical cross-section having the axis length ratio suggested by Sandler and Dodge (1968). In all these studies values of material properties are estimated from experimental results or from analysis of simpler ellipsoidal models.

Since some indication of the material properties of the myocardium can be obtained from simple elliptical methods, it initially seemed possible that a more comprehensive account might be derived from the use of finite element methods. This approach, described in detail elsewhere (Vinson, 1977), was not fruitful. Though the finite element technique can be adapted for use in this way, it became apparent that the equations were ill defined and needed large amounts of data not readily available and that values of the material properties obtained were critically dependent on the deflections measured.

A different approach was, therefore, used in the present study which was aimed at identifying some of those factors which might be of clinical significance. The initial data were insufficient to obtain a unique set of values of material properties so that estimates were aimed at by an iterative process and comparison with the angiograms. The estimates are thus consistent with the angio data, but not necessarily unique. Using these as a basis we have explored the effects of changes in these initial material properties on the predicted angiographic outlines. The results of studies of this type are not directly applicable to the individual patients. Instead, they indicate that when structures whose shape approximates to that of an actual left ventricle rather than to some idealised geometrical figure are considered to operate over observed ranges of diastolic pressure, then variation of diastolic wall properties within a range that has some experimental basis causes changes in wall deflection that can be measured using standard clinical methods. In the present study, we have attempted to identify sources of variation that produce the most significant alterations in these deflections. The results must not be equated with experimental observation, but can, perhaps, be used to suggest areas in which more direct measurement is likely to be fruitful in understanding cardiac function.

The procedure described above leads to a number of conclusions of potential clinical significance. The mitral annulus appears to have an appreciable influence on left ventricular diastolic wall movement. This may have practical importance after mitral valve replacement. At present, a variety of mechanical prostheses or heterografts are used, but all these have in common is a rigid mitral valve ring. Abnormal left ventricular wall movement has previously been documented after mitral valve replacement (Miller *et al.*, 1973; Sutton *et al.*, 1977): septal movement is reversed and the peak rate of increase of left ventricular dimension is reduced. This abnormal pattern of filling is not seen should a paraprosthetic leak develop, and it does not occur after mitral valve repair, when the ring is supported by two discontinuous sutures. Though changes in the diameter of the mitral valve ring have not been reported in man, they have been described in postmortem specimens arrested at different stages of the cardiac cycle by Lian (1909). If a mitral prosthesis could be designed without a rigid ring, it might have significant haemodynamic advantages.

The material properties of the myocardium are complex. Three of these may merit further study in view of their possible effect in determining left ventricular wall position during diastole: the degree of anisotropy, variation in shear modulus, and in particular the spiral arrangement of the muscle fibres. These factors probably reflect the high degree of organisation of the normal left ventricle, which has been little studied in man owing to the difficulty in gaining information *in vivo*. Nevertheless, its effects on left ventricular function appear so profound that conclusions based on models in which the myocardium is assumed to be homogeneous and isotropic are seen to be of limited value, and further attempts to supply the necessary information appear essential. It is also apparent that the stress pattern within the myocardium is complex, and that it is not possible to use a single cross-section to describe it. This is of significance in attempting to derive material properties *in vivo*, as has previously been pointed out, and also in attempting to understand the very much more difficult problem of describing systolic events.

The conclusions regarding myocardial infarcts may also have clinical significance, particularly those dealing with fibrous scars. Previous observations have suggested that the properties of the cavity may change after myocardial infarction, with an increase in stiffness (Bristow *et al.*, 1970), as predicted by the present results. It also appears that the physiological effects of an infarct depend not only on its size and intrinsic properties, but also on its site within the ventricle. The disturbance to filling appears to be greater when the basal region is involved than when the infarct is apical. It should be possible to investigate this difference clinically. Finally, the results suggest that a localised region of abnormal wall properties need not necessarily lead to an abnormality of wall movement confined to the same site, but that such disturbances may be more generalised, affecting wall movement elsewhere in the cavity. This conclusion is potentially significant if attempts are made to localise abnormalities of wall movement in patients with single vessel coronary artery disease. The present results suggest that this assumption might be premature.

This study has many limitations. The possible effects of right ventricular pressure, pericardial pressure, or the mitral subvalve apparatus on left ventricular wall movement were not investigated. Angiography is not a wholly satisfactory method in defining end-systolic wall movement, and a comprehensive description of left ventricular wall position cannot be obtained from views in only two planes. Measurements of wall thickness were limited to a small region on each cine frame. The interventricular septum almost certainly has a structure different from that of free wall, and should be modelled separately. It is possible that two-dimensional echocardiographic methods might be useful as a supplement to angiography, particularly to gain a more comprehensive description of the distribution of wall thickness, while, in the more distant future, computerised tomography or related methods may be of value.

Finite element methods may suggest further possibilities of clinical significance. At present, their use has significant limitations in routine clinical practice, particularly in respect to the relatively limited amount of information available to construct the model, and the amount of computation involved. In spite of this, however, they may be helpful in exploring the implications of myocardial structure and properties on overall left ventricular function, and in giving some insight into the relation between the two which cannot easily be appreciated when simpler methods are used.

We acknowledge with thanks a generous grant from May and Baker towards computing equipment.

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Detection of postinfarction left ventricular aneurysms by first pass radionuclide ventriculography using a multicrystal gamma camera[1]

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SUMMARY Eighteen patients with a history of previous anterior myocardial infarction and suspected left ventricular aneurysms were studied both by contrast left ventriculography and by first pass radionuclide ventriculography using Technetium^{99m} and a computerised multicrystal gamma camera. The radionuclide study successfully identified all 14 patients with aneurysms and all 4 with diffusely hypokinetic ventricles. Ejection fraction calculated from the change in radioactive counts in the left ventricle correlated well with that calculated from the area-length method from the contrast angiogram ($r = 0{\cdot}83$).

Ventricular volumes calculated from the area-length formula for both contrast and radionuclide angiograms correlated closely ($r = 0{\cdot}85$ and $r = 0{\cdot}89$ for end-systolic and end-diastolic volumes, respectively). In the 14 patients with aneurysms, there was a close correlation between the extent of akinesis, as assessed by the two methods ($r = 0{\cdot}94$). The ability of the radionuclide ventriculogram to provide accurate information on global and segmental ventricular function, and to differentiate between segmental and diffuse ventricular dysfunction, enables the method to act as a screening procedure in the investigation of patients with suspected left ventricular aneurysms.

Left ventricular failure or congestive cardiac failure after myocardial infarction may be the result of a localised left ventricular aneurysm or of global ventricular hypokinesis (Bruschke *et al.*, 1973). The differentiation between these two derangements of ventricular function is crucial in the assessment of such patients, as those with diffuse hypokinesis are rarely aided symptomatically by coronary artery bypass grafting or surgical resection. In addition, the operative mortality is high in this group, and operation is not recommended. Those with segmental dysfunction, however, are often candidates for surgical resection, and may show an improvement in left ventricular function after aneurysmectomy (Favaloro *et al.*, 1968; Key *et al.*, 1968; Graber *et al.*, 1972; Mundth *et al.*, 1972). The differentiation between diffuse and segmental disorders of ventricular contraction has been successfully accomplished for some years by cardiac catheterisation and contrast angiography (Baron, 1971; Hamilton *et al.*, 1972).

Radioisotope techniques employing imaging of the radioactive cardiac blood pool at equilibrium, and using end-systolic and end-diastolic electrocardiographic gating, have been previously reported as able to detect regional left ventricular dysfunction (Strauss *et al.*, 1971; Zaret *et al.*, 1971; Rigo *et al.*, 1974). There are, however, some inherent disadvantages of these techniques, in particular the high background counts within the other cardiac chambers, the need for electrocardiographic gating devices, and limitation of choice of projection caused by inadequate separation of the cardiac chambers in the right anterior oblique view.

Another approach to radionuclide cineangiography is the first pass technique, in which only a single pass of an intravenously injected bolus of a radionuclide is imaged in transit through the individual cardiac chambers and lungs. In dynamic cardiac studies, three components in the resolution of an imaging system must be considered, (a) temporal, or the rate of framing, (b) spatial, and (c) statistical, or data density, and these components are not mutually independent. Fast framing rates to

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improve temporal resolution, without an increase in count rate capabilities, will decrease statistical accuracy and impair the ability of the system to detect abnormalities.

With conventional single crystal gamma cameras, the count rate and time-response capabilities are insufficient to provide statistically accurate data from the first pass. Though the count rates achieved may be sufficient to determine ejection fraction, they are often inadequate to define the ventricular borders precisely, or to analyse regional wall motion (Pitt and Strauss, 1977).

Using a multicrystal gamma camera (Bender and Blau, 1963), however, high count rate capabilities may be achieved (Grenier *et al.*, 1974), with framing rates of 20 per second. The time resolution of 50 milliseconds is necessary to achieve accurate frames of each phase of the cardiac cycle. At longer count intervals, a frame that is designated end-diastole may already contain early systolic elements, and hence temporal resolution will be impaired. Such a combination of high temporal and statistical resolution allows accurate data to be acquired from the first pass.

This paper describes the results and correlations with cineangiographic data in 18 patients with suspected left ventricular aneurysms.

Patients and methods

Eighteen patients underwent cardiac catheterisation and left ventricular angiography for suspected left ventricular aneurysms. All had previously documented anterior myocardial infarctions. There were 15 men and 3 women, with a mean age of 57 years and a range of 44 to 69 years. The time elapsed from infarction to investigation was 1 month to 8 years, with a mean of 16 months and the principal reason for investigation was heart failure in 7, angina pectoris in 7, and ventricular arrhythmias in 4. All patients had a full clinical history taken and examination performed on admission, and all had standard 12 lead electrocardiograms and standard inspiratory upright posteroanterior chest *x*-ray films.

At cardiac catheterisation, contrast angiography was performed in the right anterior oblique projection. End-diastolic and end-systolic frames from the cineangiogram were visually selected, ignoring ectopic and immediately post-ectopic beats, and subsequently enlarged. The outline of the ventricular perimeters at end-diastole and end-systole were traced onto a graphic tablet with a pressure sensitive surface linked on-line to a computer (Honeywell DDP 516) which calculated the areas by an algorithm analogous to planimetry. The use of this system for measuring areas has already been described in another clinical context (Ward *et al.*, 1976). The long axes of the ventricles and the length of the end-diastolic perimeters were measured also. End-diastolic and end-systolic volumes were then calculated from the prolate spheroid model formula for single plane right anterior oblique angiograms (Greene *et al.*, 1967).

For the radionuclide study, the patient was positioned in the right anterior oblique projection, under the multicrystal detector of a Baird-Atomic system 77 gamma camera. An 18 gauge cannula was introduced into a medial vein of the cubital fossa under local anaesthetic, and attached to a 10 cm polyethylene tube with a 0·5 ml capacity, separated by a three-way stopcock from a 20 ml syringe full of normal saline. A bolus of high specific activity Technetium^{99m}, as pertechnetate, was injected with a rapid 20 ml saline flush. The dose of radionuclide varied from 8 to 15 mCi, in a volume of 0·05 to 0·2 ml. The site of vein chosen is important, as injection of the bolus into lateral veins is associated with a longer path to the heart, and collateral vessels may conduct the bolus to the heart at different rates. Two or more separate components thus occur, with loss of bolus integrity (Watson *et al.*, 1973).

One thousand frames of data were collected over a period of 50 seconds, that is at 50 millisecond framing intervals, to record the first pass of the bolus through the individual cardiac chambers and lungs. The data were recorded directly onto computer disc memory. This imaging system employs an array of 294 sodium iodide crystals arranged in a matrix of 14 × 21, and for the dynamic first pass studies a one-inch parallel hole collimator was used. The multicrystal detector achieves high photon count rates of 200 000 counts per second (Schad, 1977). No electrocardiographic signal was recorded during the study.

After data acquisition, corrections for field non-uniformity and the dead-time of the instrument were applied.

The study was then played back as a sequential series of 12 images, showing the position of the bolus at 1·5 second intervals (Fig. 1), and a region of interest flagged to include the entire left ventricle. A high frequency histogram of counts against time for the left ventricular phase was generated (Fig. 2) to display the fluctuations in radioactive counts occurring with each heart beat. Each individual peak and trough represents the end-diastolic and end-systolic counts respectively for an individual cardiac cycle. The counts are proportional to the volume of the ventricle at any moment, and therefore ejection fraction may be calculated from the formula:

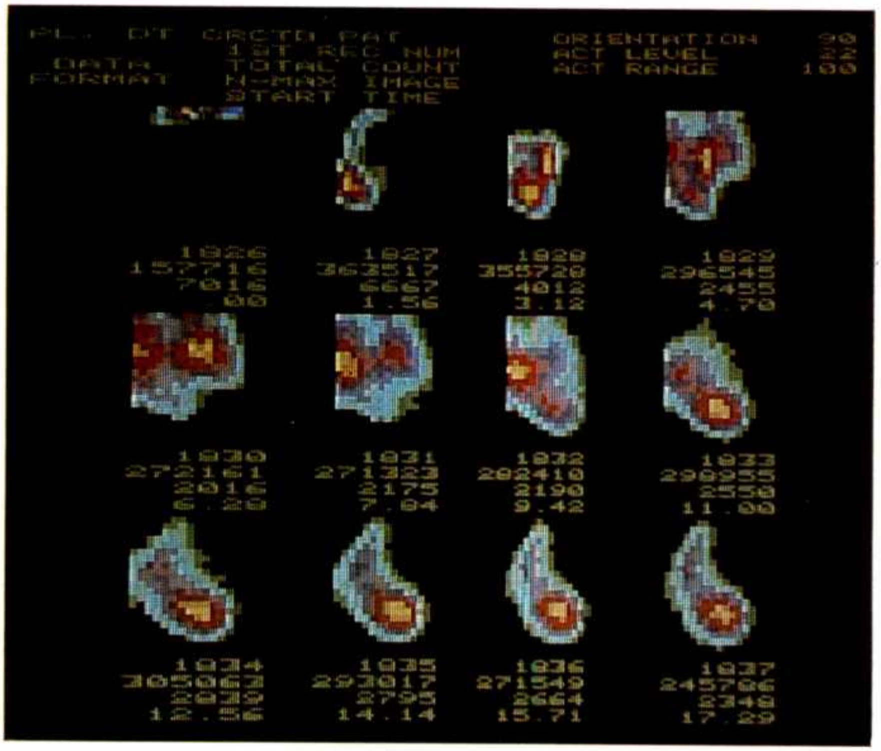
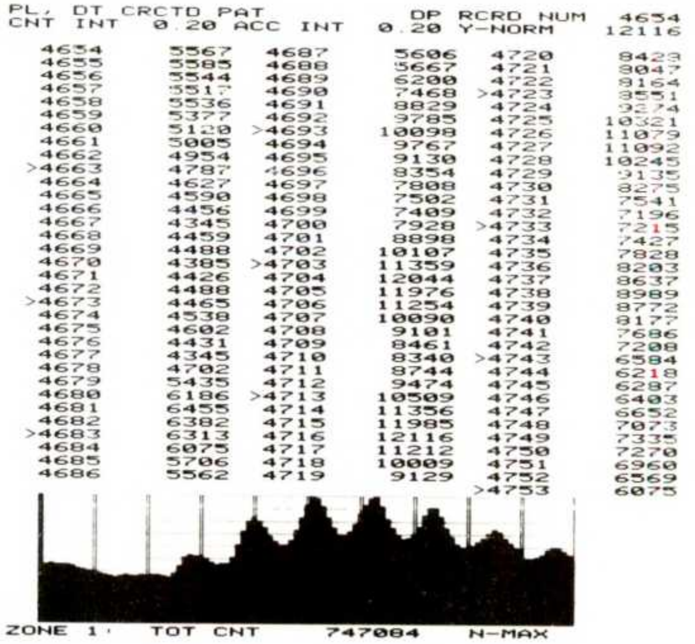


Fig. 1 *Serial images at 1·5 second intervals after injection of the bolus, showing the passage of the bolus through the right heart and lungs (first 5 frames) and subsequent entry into the left atrium and left ventricle.*



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CNT INT    0.20 ACC INT        0.20 Y-NORM        12116

  4654       5567    4687       5606    4720       8423
  4655       5585    4688       5667    4721       8047
  4656       5544    4689       6200    4722       9164
  4657       5517    4690       7468   >4723       8551
  4658       5536    4691       8829    4724       9274
  4659       5377    4692       9785    4725      10321
  4660       5120   >4693      10098    4726      11079
  4661       5005    4694       9767    4727      11092
  4662       4954    4695       9130    4728      10245
 >4663       4787    4696       8354    4729       9135
  4664       4627    4697       7808    4730       8275
  4665       4590    4698       7502    4731       7541
  4666       4456    4699       7409    4732       7196
  4667       4345    4700       7928   >4733       7215
  4668       4459    4701       8898    4734       7427
  4669       4488    4702      10107    4735       7828
  4670       4385   >4703      11359    4736       8203
  4671       4426    4704      12044    4737       8637
  4672       4488    4705      11976    4738       8989
 >4673       4465    4706      11254    4739       8772
  4674       4538    4707      10090    4740       8177
  4675       4602    4708       9101    4741       7686
  4676       4431    4709       8461    4742       7208
  4677       4345    4710       8340   >4743       6584
  4678       4702    4711       8744    4744       6218
  4679       5435    4712       9474    4745       6287
  4680       6186   >4713      10509    4746       6403
  4681       6455    4714      11356    4747       6652
  4682       6382    4715      11985    4748       7073
 >4683       6313    4716      12116    4749       7335
  4684       6075    4717      11212    4750       7270
  4685       5706    4718      10009    4751       6960
  4686       5562    4719       9129    4752       6569
                                       >4753       6075

ZONE 1   TOT CNT      747084     N-MAX
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Fig. 2 *High frequency time-activity histogram of counts in the left ventricle displayed at 50 millisecond intervals, over a period of 5 seconds. The arrows opposite the frame numbers and the thick vertical lines on the histogram represent 0·5 second intervals. The background correction is obtained from the data before the appearance of the peaks and troughs (frames 4654-4673). End-diastolic frames used in ejection fraction calculation are 4693, 4704, 4716, 4727, and the end-systolic frames are 4686, 4699, 4710, 4721, 4732.*

Ejection fraction = end-diastolic counts in left ventricle − end-systolic counts in left ventricle, ÷ end-diastolic counts in left ventricle − background counts.

The background correction was obtained from the frames of digital data approximately 0·5 seconds before the initial laevophase (Fig. 2) (Marshall *et al.*, 1976). After ejection fraction calculation, the individual beats surrounding the peak of the histogram were summed by the computer, the number of beats usually varying from 4 to 8. The summed cardiac cycles were then displayed as a cineangiogram of one average or representative cardiac cycle, allowing subsequent analysis of wall motion.

Single frames of the cine-cycle were then displayed as frozen images and processed by addition, subtraction, multiplication, or division with other frames, for generation of the perimeters of the ventricle, superimposition of the perimeters, or display of stroke volume distribution. No assumptions about ventricular shape are made during ejection fraction calculation.

The perimeters from the radionuclide ventriculogram were then traced onto the same pressure sensitive graphic tablet as those from the contrast angiograms, for computations of areas and lengths allowing ventricular volumes to be calculated.

The pattern of left ventricular contraction was analysed according to whether or not global or segmental dysfunction was present.

An aneurysmal ventricle was defined as one in which an akinetic segment could be shown, clearly demarcated from a contractile segment, in sinus rhythm. A diffusely hypokinetic ventricle was one in which poor wall motion occurred globally and where no clear-cut demarcation could be made between akinetic and non-akinetic muscle. In the group with left ventricular aneurysms, the extent of wall motion defect produced by the aneurysm was quantified for both contrast and isotope ventriculograms by expressing the length of the akinetic segment as a percentage of the total end-diastolic circumference of the ventricle (Feild *et al.*, 1972). Thus the akinetic segment percentage (AS%) =

Table *Clinical, electrocardiographic, and chest* x-ray *data from the 18 patients, with the angiographic and radionuclide classification of aneurysm or diffuse hypokinesis*

Case no.	*Time from infarct to investigation*	*Main reason for investigation*	*Abnormal praecordial impulse*	*S_3 or S_4*	*Systolic murmur*	*Site of ECG Q waves*	*Persistent ST elevation*	*CTR > 50%*	*Bulge on chest x-ray*	*Aneurysm (A) contrast*	*or Hypokinesis (H) radionuclide*
1	1 year	LVF	+	+	−	V_1–V_5	+	+	−	A	A
2	6 months	Angina	+	+	−	II, III, aVF V_2–V_6	−	+	−	A	A
3	1 month	Angina	+	+	−	V_1–V_5	+	+	−	A	A
4	2 months	Recurrent ventricular tachycardia	−	−	−	V_1–V_4	+	−	−	A	A
5	5 months	Angina	+	+	+	V_2–V_5	+	+	−	A	A
6	1 year	Ventricular tachycardia	−	−	−	I, V_2–V_6	+	+	−	A	A
7	2 months	LVF	−	+	−	I, aVL V_2–V_6	+	−	−	A	A
8	4 months	Angina	+	+	−	I, aVL V_4–V_6	+	+	−	A	A
9	2 years	LVF	+	+	+	V_1–V_4	+	+	−	A	A
10	2 months	Ventricular tachycardia and fibrillation	+	+	+	V_1–V_6	−	+	+	A	A
11	5 years	LVF	+	+	−	I, aVL V_1–V_6	+	+	+	A	A
12	8 years	Angina	+	+	+	II, III, aVF V_2–V_6	+	+	−	A	A
13	3 months	Angina	+	+	+	I, aVL V_1–V_6	+	+	+	A	A
14	18 months	LVF	−	+	+	II, III, aVF V_3–V_6	+	+	−	A	A
15	2 years	LVF	+	+	+	RBBB V_1–V_5	−	+	−	H	H
16	9 months	Ventricular fibrillation	−	+	−	LBBB at investigation	−	+	−	H	H
17	15 months	LVF	+	+	+	II, III, aVF V_2–V_6	+	+	−	H	H
18	1 year	Angina	−	+	+	II, III, aVF V_3–V_6	+	+	−	H	H

S_3/S_4, 3rd or 4th heart sounds; CTR, cardiothoracic ratio; LVF, left ventricular failure; RBBB/LBBB, right or left bundle-branch block.

(akinetic length of the end-diastolic circumference ÷ end-diastolic circumference) × 100.

All measurements were made in the right anterior oblique projection, and radionuclide studies were carried out within 6 hours before cardiac catheterisation in 14 patients, and within 24 hours in the remaining 4.

Results

CLINICAL DATA

The Table summarises clinical, electrocardiographic, and *x*-ray findings, along with the angiographic and radionuclide classification into the aneurysm group or hypokinesis group. Of the 14 patients with aneurysms 10 had abnormal praecordial cardiac impulses (71%), while of the 4 with diffuse hypokinesis 2 had abnormal impulses (50%) which would have been consistent with an aneurysm. On auscultation, 12 in the aneurysm group had either a third or fourth heart sound (86%) and 6 (43%) had apical systolic murmurs. All 4 with diffuse hypokinesis had third or fourth heart sounds, and 3 (75%) had systolic murmurs.

All 14 in the aneurysm group had electrocardiographic evidence of previous anterior infarction, and 3 had evidence of additional inferior infarction. Persistent ST segment elevation of 1 mm or more in at least one electrocardiographic lead was present in 12 (86%). Of those with diffuse hypokinesis, electrocardiograms showed anterior and inferior infarction in 2, anterior infarction with right bundle-branch block in 1, and at the time of investigation, left bundle-branch block in 1, though previous anterior myocardial infarction had been electrocardiographically documented. Two patients (50%) had persistent ST segment elevation.

Chest *x*-ray films showed a cardiothoracic ratio of more than 50 per cent in 12 of the patients with aneurysms (86%), and 3 had a definite bulge on the cardiac silhouette suggesting an aneurysm. All 4 with diffuse hypokinesis had increased cardiothoracic ratios, but none had abnormal bulges.

At cardiac catheterisation, none of the 18 patients had significant mitral regurgitation on contrast angiography. All 14 with left ventricular aneurysms had aneurysms demonstrated by the first pass radionuclide study, and the latter successfully identified all with contrast angiographically proven diffuse hypokinesis.

Mean ejection fraction calculated from the change in radioactive counts in the left ventricle was 26 per cent, and that calculated geometrically from the contrast angiogram was 23 per cent. Fig. 3 shows graphically the correlations in ejection fraction, and even allowing for the difference in techniques, and the low levels of ejection fraction in this group of patients, there is a significant correlation, with r = 0·83. Only 17 points appear on Fig. 3, as 2 patients had identical ejection fractions from contrast and isotope studies, of 23 per cent and 17 per cent respectively, and thus 2 points are superimposed.

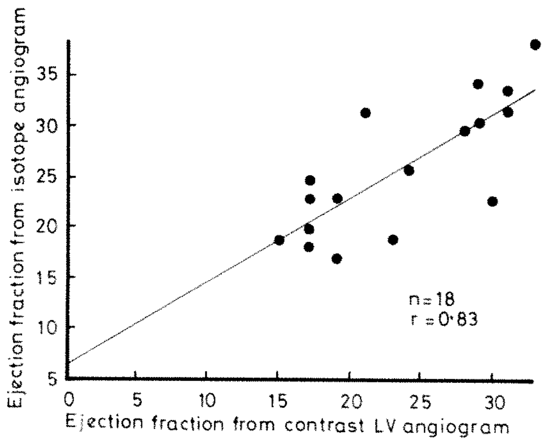


Fig. 3 *Plot of left ventricular ejection fraction (LVEF) obtained by the area length method from contrast angiograms, versus radionuclide LVEF obtained by changes in left ventricular counts.*

The patients with aneurysms could not be differentiated from those with diffuse hypokinesis on the basis of ejection fraction alone.

Fig. 4a and 4b are examples of end-diastolic and end-systolic frames from the contrast angiogram of a patient with a ventricular aneurysm, together with the superimposed end-diastolic and end-systolic perimeters traced from the angiogram (Fig. 4c) and the superimposed perimeters from the first pass study in the same patient (Fig. 4d). In the isotope study, the purple perimeter represents end-systole and the white end-diastole. In both contrast and radionuclide studies there is inward motion of the ventricle apparent at the base of the heart but the perimeters show no motion anteroapically, providing the typical angiographic appearance of an anterior ventricular aneurysm.

Fig. 5a-d show the same sequence of information from a patient with diffuse hypokinesis. In both contrast and isotope studies poor inward wall motion is apparent globally, and no localised or segmental defect is visible.

Actual stroke volume counts can be obtained by subtraction of end-systolic from end-diastolic counts. Further subtraction of the stroke volume counts from the end-systolic frame allows a visual representation of residual volume and stroke

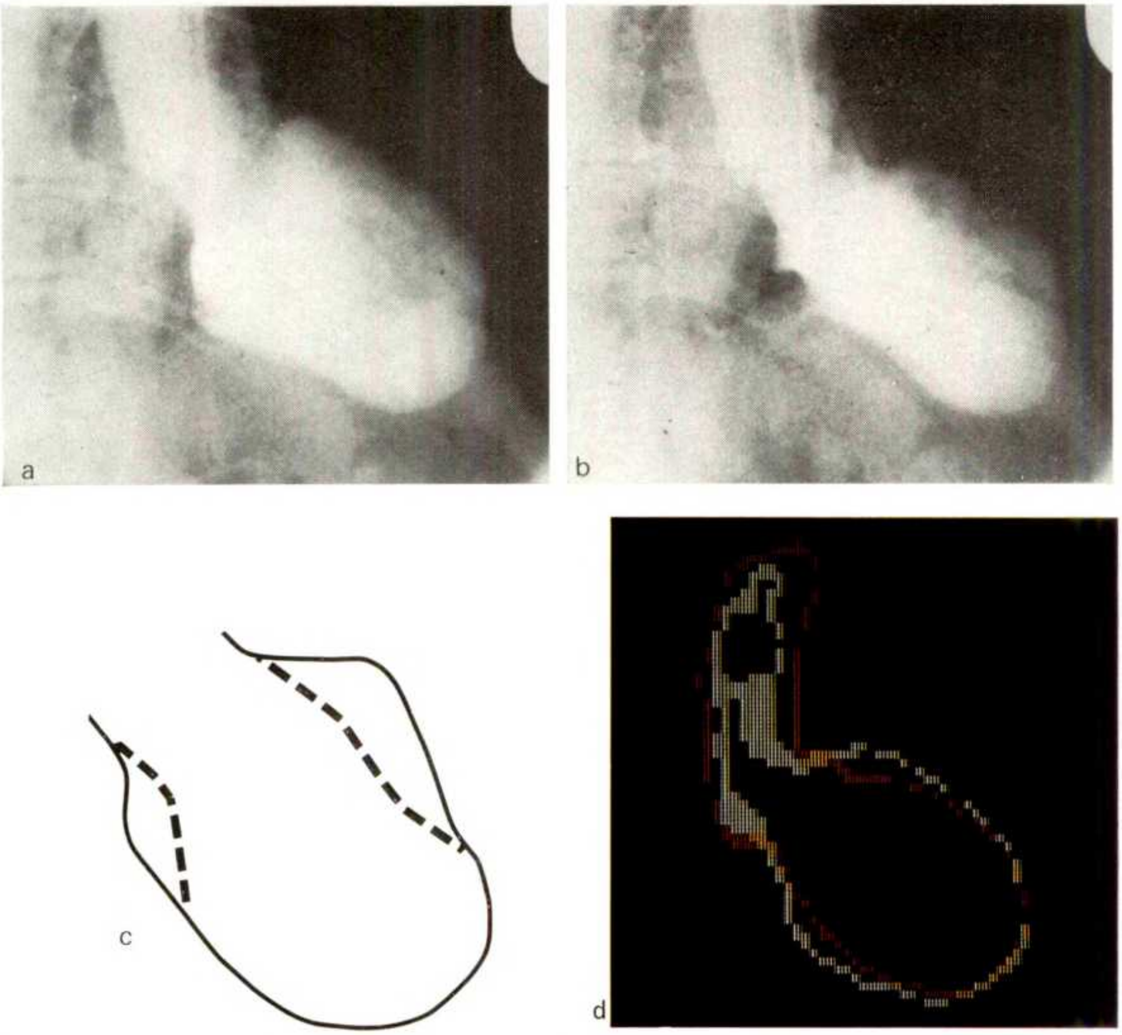


Fig. 4 (a) *End-diastolic frame from cineangiogram of a patient with a left ventricular aneurysm.* (b) *End-systolic frame from same cineangiogram.* (c) *End-diastolic (solid line) and end-systolic (dotted line) perimeters from the cineangiogram, traced and superimposed.* (d) *Superimposed end-diastolic (white) and end-systolic (purple) perimeters from the radionuclide angiogram of the same patient. Note the basal inward motion of the perimeters, with akinesis anteroapically, in both contrast and isotope studies.*

volume distribution. Fig. 6 shows such data from a patient with an aneurysm and one with diffuse hypokinesis. The end-diastolic perimeter is added in each case. The dark areas inside the perimeter represent those areas from which the stroke volume has been ejected and the coloured areas the residual counts within the ventricle. The colour display of the system reproduces the activity distribution in 16 colour shades, from dark green (6·25%) to bright yellow (100%).

The residual counts in the aneurysm example are apparent, situated in the apical segment of the ventricle only, while the basal segment is empty of counts. In the diffusely hypokinetic ventricle residual volume is evenly distributed, not segmentally. Such information on stroke volume distribution is able to provide additional data to that obtained from inspection of superimposed perimeters, as the latter reflects only two dimensional changes in ventricular wall position, whereas

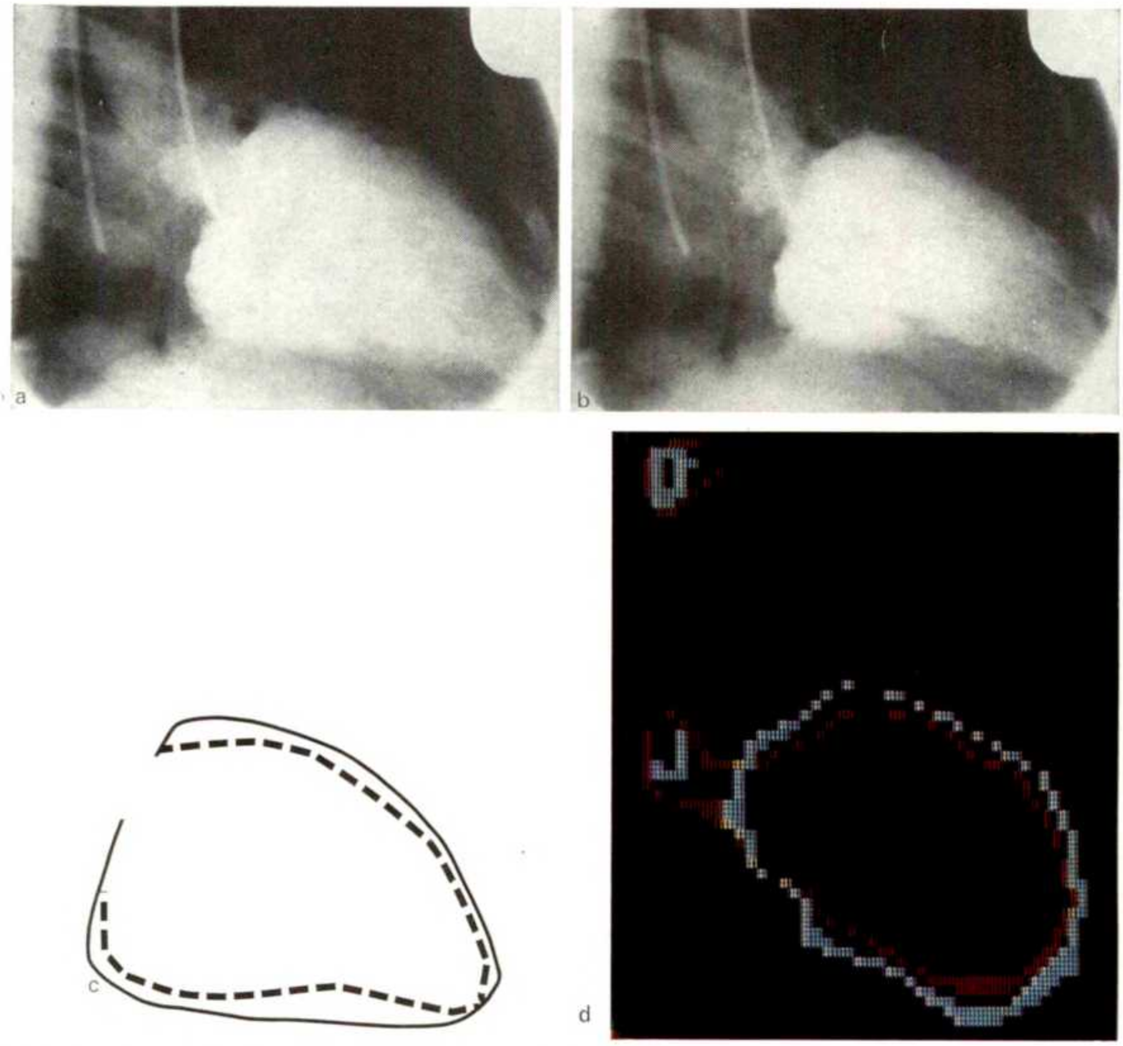


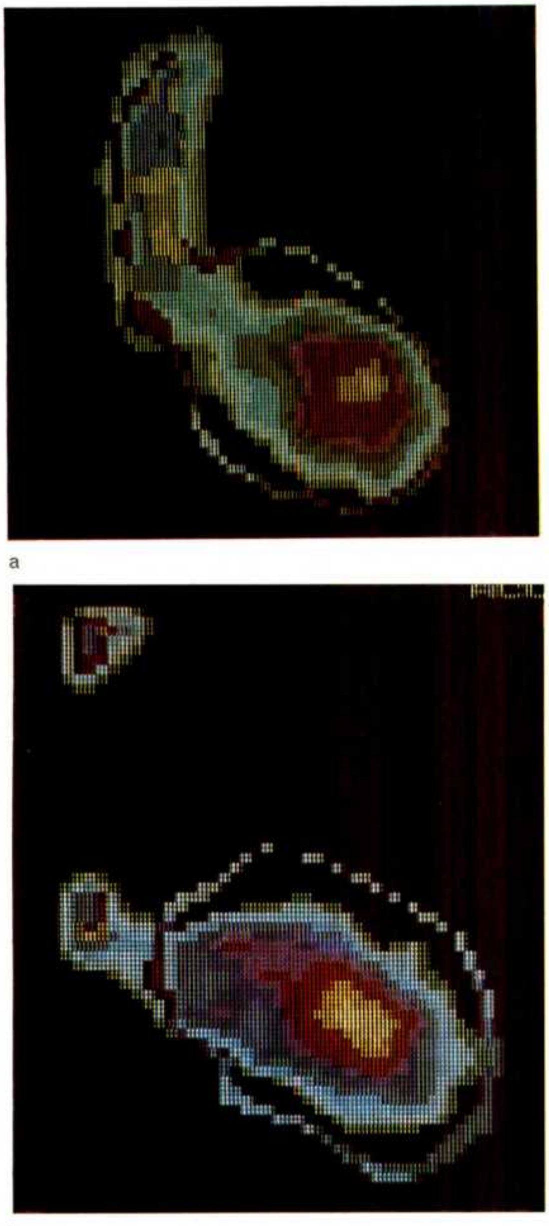
Fig. 5 (a) to 5 (d) *Same sequence of data as in Fig. 4, for a patient with diffuse ventricular hypokinesis. Both contrast and radionuclide studies show generalised poor inward wall motion, with no segmental dysfunction.*

stroke volume is in a three dimensional distribution, and contributions of other segments of the ventricle, not visualised in the right anterior oblique projection, to stroke volume may be assessed. This is apparent when one compares, for example, the radionuclide angiogram perimeters in Fig. 5d with the stroke volume distribution in Fig. 6b.

In 17 patients in whom adequate measurements could be made, end-diastolic and end-systolic volumes were calculated from the traced perimeters of the isotope angiogram, using the area-length method and the known magnification factor for the multicrystal detector. The mean end-diastolic volume was 282 ml and 297 ml for the contrast and radionuclide ventriculograms, respectively. Mean end-systolic volumes were 218 ml and 234 ml, respectively. Fig. 7 shows the correlations between the volumes in graphic form, and though there is a tendency for the isotope values to overestimate the volumes when compared with those from the contrast angiograms, the correlations are nevertheless significant, $r = 0{\cdot}89$ and $r = 0{\cdot}85$ for end-diastolic and end-systolic volumes, respectively, with regression equations of:

$y = 0{\cdot}92x + 38$ ml for end-diastolic volume

$y = 0{\cdot}85x + 48$ ml for end-systolic volume.


a

b

Fig. 6 (a) *Stroke volume distribution in a patient with ventricular aneurysm. Stroke volume counts are subtracted from end-systolic counts, and end-diastolic perimeter (EDP) is added. The black areas inside the EDP indicate the basal regions of ventricle from where counts have been removed, and the coloured area the distribution of residual volume, which here occupies the aneurysmal section only.* (b) *The same for a patient with diffuse hypokinesis. Stroke volume and residual distribution are of a non-segmental nature.*

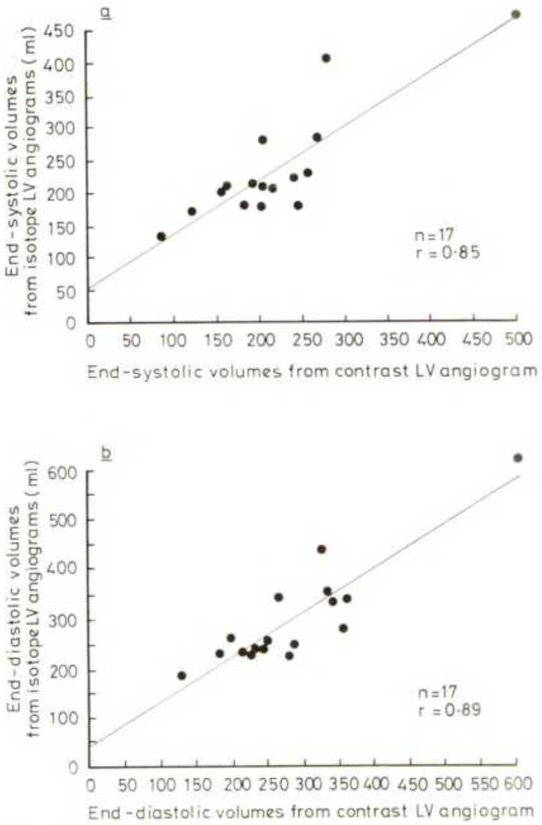


Fig. 7 (a) *Plot of end-systolic volumes.* (b) *End-diastolic volumes obtained from the area length method for contrast and radionuclide ventriculograms.*

In the 14 patients with proven aneurysms, the extent of wall motion defect produced by the aneurysm was expressed, as outlined above, as a percentage of the total end-diastolic circumference.

Fig. 8 shows the correlation between the akinetic lengths for contrast and isotope ventriculograms which is extremely good, covering a range from 22 to 70 per cent of ventricular circumference, with r = 0·94.

CORONARY ARTERIOGRAPHIC FINDINGS

Of the 14 patients with ventricular aneurysms, all had either a completely occluded left anterior descending coronary artery or a severe stenosis of 80 per cent or more. Seven patients had single vessel disease, 1 had a blocked left anterior descending and an aneurysm of the circumflex artery, 2 had left anterior descending and right coronary artery lesions, and 4 had three-vessel disease. Selective coronary arteriography was performed in

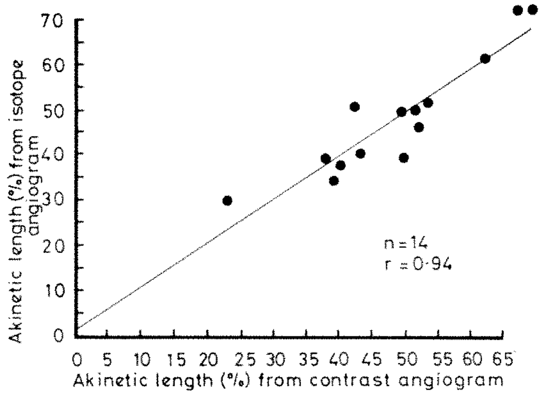


Fig. 8 *Plot of extent of akinesis from contrast and radionuclide ventriculograms.*

2 patients with diffuse hypokinesis, and both had three-vessel disease. In the other 2, cardiac catheterisation was terminated after the left ventricular angiogram had shown ventricular hypokinesis.

Discussion

The differentiation between segmental ventricular dysfunction and diffuse ventricular hypokinesis has for some years been successfully accomplished by cardiac catheterisation and selective left ventriculography (Baron, 1971; Hamilton *et al.*, 1972). Recently, noninvasive techniques such as M-mode echocardiography have been applied in attempts to diagnose left ventricular aneurysms (Dillon *et al.*, 1976), though it is not yet proven that ventricular aneurysms may be differentiated from diffuse ventricular hypokinesis by this technique.

Detection of left ventricular aneurysms by gated blood pool scans has been previously described (Rigo *et al.*, 1974) but the drawbacks to this particular approach to nuclear angiography are many. Imaging is only carried out at the extremes of the cardiac cycle, so much data are discarded. Electrocardiographic gating is employed, and imaging is carried out only during the immediate 40 milliseconds associated with end-systole, and 60 milliseconds associated with end-diastole (Zaret *et al.*, 1971). As there is insufficient activity in any single brief period of imaging, the activity from several hundred cardiac cycles must be summed to achieve enough counts for statistical accuracy, and imaging may take up to 10 minutes. Numerous pitfalls may occur inasmuch as the patient may not be haemodynamically stable for that length of time, and if electrical and mechanical events become deranged, the exact siting of the electrocardiographic gate may be inaccurate, and may vary from one beat to another. Recent reports have described an extension of this simple gating to provide multiple gated blood pool imaging, allowing more of the cardiac cycle to be displayed (Sneed *et al.*, 1977; Strauss *et al.*, 1977). Nevertheless, variations from beat to beat in the association of electrical and mechanical events may still introduce an error. Right anterior oblique imaging of the radioactive blood pool at equilibrium makes background corrections difficult because of high background counts in the right ventricle lying anterior to the left ventricle, interfering with left ventricular count analysis. Since right anterior oblique cineangiograms are those most often employed when biplane facilities are not available, and since the right anterior oblique projection is superior to the left anterior oblique at detecting asynergy (Cohn *et al.*, 1974), then right anterior oblique studies are optimal for allowing direct comparisons between contrast and radionuclide techniques in the detection and quantification of asynergy. The first pass radionuclide ventriculogram allows right anterior oblique projections to be performed with low background counts in the right ventricle, as the bolus will have been ejected from the right ventricle before entering the left. The first pass technique requires only 50 seconds for data acquisition and requires no electrocardiographic gating, as end-diastolic and end-systolic frames are selected entirely by count density within the ventricle, as manifest by the peaks and troughs in the histogram of Fig. 2. Patient stability is only necessary for the few cardiac cycles utilised in the first pass, and no assumptions are made as to the temporal relations of systole and diastole to electrical events.

The correlations in ejection fraction obtained (Fig. 3) are significant even at this low end of the spectrum of ventricular function, but nevertheless, despite the significant correlations, the graph shows a degree of scatter which can be accounted for, at least in part, by deviations from the prolate spheroid model of distorted and aneurysmal ventricles, and subsequent errors in volume calculations from the contrast angiogram. Good correlations between ejection fractions calculated by such diverse methods have been previously reported (Sneed *et al.*, 1977) though in this latter study comparisons were made between left anterior oblique radionuclide studies and right anterior oblique contrast films.

Calculation of absolute ventricular volumes from the radionuclide study requires the same assumptions about ventricular geometry as apply to the contrast angiogram, and the same subjective outlining of perimeters. Nevertheless, by applying the prolate spheroid model to both techniques, however invalid that model may be in this group of patients, the errors will apply to both techniques and should tend to cancel each other out. The correlations are significant (Fig. 7) though there is a tendency for the radionuclide study to overestimate the volumes compared with those from the contrast film. Small errors in choosing the exact edge of the ventricular outline will be cubed using the prolate spheroid model, and generation of the perimeters of the ventricle from the isotope study is achieved by edge enhancement of the activity at the left ventricular border. Small errors here will also compound the errors in volume calculation.

Despite these pitfalls, the isotope ventriculogram has yielded good correlations, similar to those reported by gated blood-pool scanning (Strauss *et al.*, 1971).

Although ejection fraction and absolute volumes provide important information on global left ventricular function, they provide no information as to segmental function. Not only is the first pass radioisotope ventriculogram able to differentiate between aneurysmal and diffusely diseased ventricles, but is also able to quantify accurately the extent of wall motion defect present (Fig. 7). Our results are similar in this respect to those of Rigo *et al.* (1974). This simple index of extent of akinesis has been shown by others to have an important bearing on the presence or absence of heart failure (Feild *et al.*, 1972), though it does not provide any information on the function of the residual, contractile segment of the left ventricle in patients with aneurysms, and there is evidence that function of the contractile segment is more important in determining the prognosis of aneurysmectomy (Arthur *et al.*, 1972; Watson *et al.*, 1975; Lee *et al.*, 1977) than the actual size of the aneurysms.

Like many other groups we have found it difficult to separate patients with aneurysms from those with diffuse hypokinesis on the basis of clinical, electrocardiographic, or radiographic findings. Symptomatically, heart failure, angina, or ventricular arrhythmias occurred in both those with aneurysms and those with diffuse hypokinesis, as in the series of Rigo *et al.* (1974). Abnormal praecordial impulses were present in 10 of 14 patients with aneurysms, and 2 of 4 with diffuse hypokinesis, but the findings are too non-specific to be of any value in differentiation (Graber *et al.*, 1972). Third and fourth heart sounds appear to be extremely common in patients with aneurysms, and also in those with diffuse hypokinesis (Table).

Persistent ST segment elevation occurred in 12/14 (86%) of the aneurysms group, and 2/4 (50%) of those with diffuse hypokinesis. The numbers in this study are too heavily weighted in favour of patients with aneurysms to make statistical comparisons, but we did not find it a valuable electrocardiographic sign in the differentiation between the two groups, in common with the findings of others (Groden and James, 1969; Rigo *et al.*, 1974). The size of the cardiac silhouette on chest *x*-ray film was abnormal in 86 per cent of the aneurysm group and 100 per cent of the diffusely hypokinetic group. It is of interest that the 2 patients with aneurysms and normal cardiothoracic ratios on *x*-ray film both had normal praecordial impulses, and one had no third or fourth heart sounds. The presence of a normal radiographic heart size with an angiographically proven aneurysm is well documented (Gorlin *et al.*, 1967; Graber *et al.*, 1972).

Although none of the 4 patients with diffuse hypokinesis had abnormal bulges seen on the plain chest *x*-ray film, only 3 of the aneurysm group (21%) had such bulges. Our findings thus agree with those of Dubnow *et al.* (1965) in that routine chest *x*-ray films rarely lead to the diagnosis of ventricular aneurysms. Others, however, have noted a higher proportion of localised bulges (Mourdjinis *et al.*, 1968; Graber *et al.*, 1972). Cardiac fluoroscopy was not employed in the present study, but has previously been shown to be of little value in the exclusion of a ventricular aneurysm (Baron, 1971).

It is evident, therefore, that some sort of angiographic technique is essential in the differentiation of the two groups. The high count rate capabilities and rapid framing rates of the multicrystal gamma camera enable statistically accurate data to be achieved from the single passage of a radioactive bolus through the heart, without saturation of the crystals and the resultant random loss of counts. The patient's condition need not be stable for more than the few seconds required for the first pass, and right anterior oblique projections may be carried out with low background counts. Repeated views need a separate bolus of radionuclide, but even 2 doses of 10 millicuries each provide a radiation dose to the patient of less than 400 millirads compared with a dose of 3900 millirads for cardiac catheterisation and angiography (Gough *et al.*, 1968). One drawback of the present technique is the high cost of the computerised multicrystal gamma camera, but the cost has to be offset against the savings achieved by demonstrating noninvasively that a particular patient has a nonsurgically treatable lesion. Other workers do not perform cardiac catheterisation and angiography on those patients with heart failure, in whom isotope ventriculography shows diffuse hypokinesis (Rigo *et al.*, 1974), and such savings in terms of hospitalisation, catheterisation, and lack of ensuing morbidity are significant.

We recommend the first pass radionuclide ventriculogram as a screening procedure in the precatheterisation phase of investigation of patients with symptoms occurring after infarction. It is not unreasonable to expect that in the future a large proportion of contrast angiograms will be replaced by this technique.

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Failure of aneurysmectomy to improve left ventricular function

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SUMMARY Biplane left ventricular angiography was performed in 22 patients with isolated obstructive disease of the anterior descending branch of the left coronary artery and with an anterior aneurysm following transmural myocardial infarction. Six patients were restudied between 6 and 10 months after aneurysmectomy. Left ventricular reserve was estimated by analysis of a spontaneous postextrasystolic beat. Using angiographic techniques a contractile section, a transitional section, and a noncontractile section were identified. From the surgical patients the excised aneurysm and a transmural needle biopsy of the transitional section were investigated by light microscopy. With increasing volumes of noncontractile and transitional sections, total end-diastolic volume ($r = 0{\cdot}81$, $P < 0{\cdot}001$) and end-systolic volume ($r = 0{\cdot}94$, $P < 0{\cdot}001$) increased linearly, while the ejection fraction decreased ($r = 0{\cdot}70$, $P < 0{\cdot}001$). No relation was found between the combined volumes of the noncontractile and transitional sections on the one hand, and the end-diastolic volume, the end-systolic volume, or the ejection fraction of the contractile section on the other hand.

After aneurysmectomy a significant decrease was found in end-diastolic volume (194 to 133 ml/m^2, $P < 0{\cdot}001$) and end-systolic volume (124 to 83 ml/m^2, $P < 0{\cdot}001$) but no change occurred in ejection fraction (35 to 37%) and left ventricular end-diastolic pressure (23 to 25 mmHg). Surgical resection included part of the transitional section, which before surgery had an average ejection fraction of 27 per cent during a normal beat, rising to 41 per cent in a postextrasystolic beat. The transitional section after surgery now formed a large akinetic area of the anterior wall. We conclude that aneurysmectomy in isolated left anterior descending artery disease with anterior aneurysm fails to improve left ventricular function because the effect of reduction of left ventricular volumes is offset by the destruction of contractile behaviour in the transitional section.

Surgical resection of ventricular aneurysm after myocardial infarction has an appreciable mortality and does not always result in dramatic postoperative improvement (Favaloro *et al.*, 1968; Key *et al.*, 1968; Aranda *et al.*, 1977). Several studies have emphasised the importance of the non-damaged myocardium on operative outcome and cardiac function after aneurysmectomy (Kluge *et al.*, 1971; Watson *et al.*, 1975). The role of the border zone of an infarcted area has not been defined as a determinant of remaining function in the area surrounding the noncontractile segment. Furthermore, little information exists about the overloading effect (Crawford *et al.*, 1971) of the aneurysmal chamber on surviving muscle. This study examined left ventricular function of the contractile, transitional, and noncontractile sections of aneurysmal ventricles before and after aneurysmectomy by biplane cineangiography. Haemodynamics were then compared with the histology of specimens and biopsy material of the noncontractile and transitional section in surgical cases.

Patients and methods

We studied 22 patients during diagnostic left heart catheterisation and coronary arteriography who had an anterior aneurysm of the left ventricle following transmural anterior myocardial infarction which had occurred 6 months to 3 years before investigation. Patients with a concomitant postinfarction mitral regurgitation proven by angiography and patients with additional obstructions of the circumflex branch of the left coronary artery or the right

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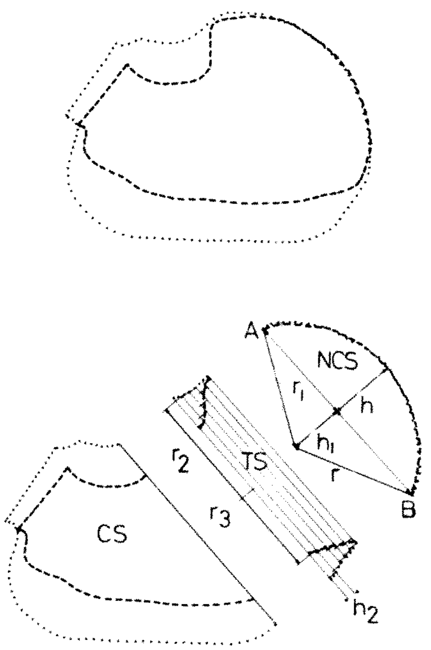
coronary artery were excluded from the series. All patients had severe obstructive lesions of the anterior descending branch of the left coronary artery. The age of the patients (1 woman and 21 men) ranged from 27 to 65 years. Six patients were restudied between 6 and 10 months after aneurysmectomy without aortocoronary bypass surgery. Another 9 patients studied because of chest pain but found to have no evidence of heart disease served as controls. The age of these patients ranged from 28 to 55 years (2 women and 7 men).

All patients were studied during routine heart catheterisation for evaluation of coronary heart disease. Propranolol and nitrates were discontinued 48 hours before investigation. Before injection of contrast material, heart rate, left ventricular systolic pressures, and end-diastolic pressures were measured (via femoral artery) using Pigtail 7F or 8F catheters and a Statham P23Db pressure transducer at mid-chest position. Left ventricular end-diastolic pressure was measured at the peak of the R wave in lead II of the electrocardiogram. In mid-inspiration (right anterior oblique projection) 50 ml of Urografin 76 were injected over a period of 2 to 4 seconds with a power syringe while biplane cineangiograms were exposed at 32 frames/second on 35 mm film. During this injection the electrocardiogram (lead II) was recorded continuously. Thereafter coronary arteriography was performed using selective injections in the right and left coronary artery system in several right and left anterior oblique views (Judkins, 1968).



$$NCS = {}^2/_3 \pi r^2 h - {}^1/_3 \pi r_1^2 h_1 \, ; \qquad EFncs = 0 \times 100\,\%$$

$$TSed = \sum_1^n \pi r_2^2 h_2 \, ; \quad TSes = \sum_1^n \pi r_3^2 h_2 \, ; \qquad EFts \frac{TSed - TSes}{TSed} \times 100\%$$

$$CSed = EDV - (TSed + NCS) ; CSes = ESV - (TSes + NCS) ; EFcs = \frac{CSed - CSes}{CSed} \times 100\,\%$$

Fig. 1 *The upper panel shows end-diastolic (dotted line) and end-systolic (interrupted line) silhouettes of the frontal plane (right anterior oblique projection) of a ventricle with a large anterior aneurysm. The lower panel shows the technique of dissection into three parts: CS, contractile section; TS, transitional section; NCS, noncontractile section. Formulae for calculation of each section are given: ed, end-diastolic; es, end-systolic; EF, ejection fraction (%).*

CALCULATIONS

Quantitative ventriculography was carried out using the area length method for biplane technique (Kasser and Kennedy, 1969). End-diastolic and end-systolic volumes were derived from the largest and smallest silhouettes corrected for magnification and x-ray distortion using the apex and the aortic root as reference points. Ventriculographic images selected for analysis were taken from the first 4 sinus beats after injection of contrast material. In addition, in 21 patients with anterior aneurysm and in 7 patients without heart disease a single spontaneous postextrasystolic beat was analysed as proposed by Hamby *et al.* (1975). In the premature beats the coupling interval, as measured from the electrocardiogram, was less than 400 ms and was followed by a compensatory pause. In patients with an anterior aneurysm three sections of the left ventricle were determined (Fig. 1): noncontractile section, transitional section, and contractile section. The noncontractile section was the area showing no contraction. The transitional section was defined as a zone showing hypokinesia which was located between the noncontractile and contractile sections.

For demarcation of sections postextrasystolic beats were used. Formulae for calculation of volumes which were derived from Kitamura *et al.* (1973) are shown in Fig. 1. Total left ventricular volumes were calculated in each instance from biplane cineangiograms, while the noncontractile and transitional sections were calculated using the frontal plane only. Ejection fraction was determined as stroke volume divided by end-diastolic volume times 100 per cent.

SURGERY

Five patients underwent aneurysmectomy because of congestive heart failure and 1 patient because of severe ventricular rhythm disturbances. Operation was done with the patient on cardiopulmonary bypass, using a disposable bubble oxygenator. Excision of the aneurysm was done as suggested by Favaloro *et al.* (1968). Direct inspection of the heart showed a demarcation between aneurysm and normal muscle. It was necessary to leave a rim of scar tissue at the edges of the resection for support of the sutures. During operation the excised aneurysm was immediately fixed in 20 per cent formaldehyde. Paraffin sections were stained with haematoxylin-eosin and elastic van Gieson for routine histological examination. In addition, transmural tissues were obtained by needle biopsy (Tru-cut biopsy needle, Travenol Lab.) from the transitional section and were fixed in buffered 6 per cent glutaraldehyde. Semi-thin sections of these biopsies were prepared and stained with alkaline toluidine blue for light microscopy.

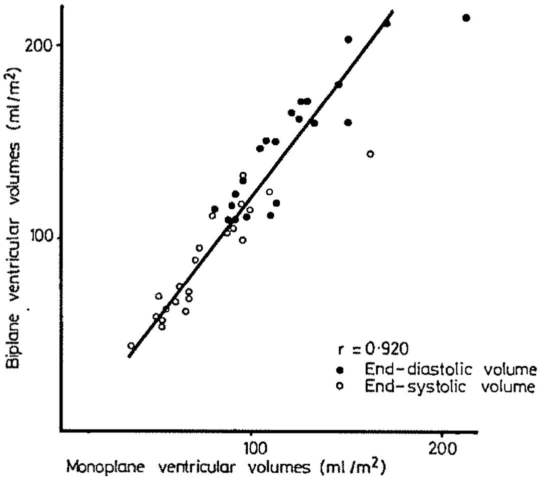


Fig. 2 *Relation between monoplane and biplane ventricular volumes for patients with ventricular aneurysms. Monoplane volumes were calculated for the sections of the ventricle as illustrated in Fig. 1 using the ellipsoid of revolution formula for contractile section.*

Results

BEFORE SURGERY

Fig. 2 compares monoplane and biplane ventricular volumes in patients with ventricular aneurysm. The monoplane volumes were calculated for the three sections noncontractile, transitional, and contractile separately. The first two sections were calculated as shown in Fig. 1. The contractile section was then calculated applying the ellipsoid of revolution formula. Summation of these 3 volumes gave the overall monoplane ventricular volumes. The biplane ventricular volumes were calculated from biplane cineangiograms. A good correlation was found using both methods ($r = 0{\cdot}920$) which confirms the validity of the techniques used. Individual data of left ventricular pressure, volume, and ejection fraction for all patients with anterior aneurysm are given in the Table. When the volume of the noncontractile section was calculated as a percentage of total left ventricular end-diastolic volume the average was 16 per cent (range 3 to 43%). When the volumes of the noncontractile plus transitional sections were calculated as a percentage of total left ventricular end-diastolic volume, the average was 39·5 per cent (range 13 to 65%). As shown in the Table, end-diastolic volumes and end-systolic volumes of patients with aneurysms were significantly higher ($P < 0{\cdot}001$) than those of controls.

Table *Individual data for heart rate (HR), left ventricular systolic pressure (LVSP), end-diastolic pressure (LVEDP), end-diastolic volume (EDVI), ejection fraction (EF) of the noncontractile (NCS), transitional (TS), and contractile (CS) section*

				Normal beat								*Postextrasystolic beat*					
				Total LV		*NCS*		*TS*		*CS*		*Total LV*		*TS*		*CS*	
Case no.	*HR bpm*	*LVSP mmHg*	*LVEDP mmHg*	*EDVI ml/m^2*	*EF %*	*EDVI ml/m^2*	*EF %*	*EDVI ml/m^2*	*EF %*	*EDVI ml/m^2*	*EF %*	*EDVI ml/m^2*	*EF %*	*EDVI ml/m^2*	*EF %*	*EDVI ml/m^2*	*EF %*
Patients with left ventricular aneurysm																	
1	74	160	41	109·1	47	2·9	0	19·2	26	86·9	53	118·2	57	19·2	40	97·5	63
2	100	160	20	115·4	49	3·3	0	22·0	11	90·0	60	150·5	67	25·2	47	121·8	73
3	71	150	14	107·6	51	3·4	0	10·4	10	93·7	58	149·9	69	14·3	45	132·1	74
4	73	144	9	123·2	63	4·3	0	26·4	48	92·3	71	126·7	71	24·6	58	97·7	78
5	55	140	18	117·7	46	6·8	0	28·0	26	82·8	56	117·5	63	29·3	44	81·3	76
6	67	145	21	150·2	53	12·1	0	27·2	44	110·7	51	158·2	60	29·0	51	117·0	69
7	80	120	20	118·5	36	13·5	0	30·7	38	74·2	42	148·5	61	36·3	42	98·6	77
8	70	125	26	211·2	41	24·1	0	58·9	30	128·0	53	248·5	56	58·7	39	165·6	70
9	90	170	14	110·8	34	16·2	0	34·2	17	60·3	53	126·8	45	40·9	32	69·7	64
10	63	112	18	129·4	48	18·0	0	27·4	18	84·0	65	137·0	63	31·0	40	88·0	84
11	72	160	28	203·7	42	31·0	0	65·3	27	107·3	63	216·1	48	70·2	35	114·8	69
12	96	100	10	165·2	42	30·4	0	47·7	35	86·9	60	173·5	52	45·3	38	97·7	75
13	63	160	20	184·8	50	34·0	0	20·4	41	130·3	65	184·8	62	20·3	52	130·0	80
14	75	120	8	118·8	44	21·9	0	13·8	21	76·0	61	130·7	59	18·9	42	89·9	77
15	81	115	10	159·6	34	32·7	0	35·6	16	91·2	53	205·3	49	40·0	27	132·5	68
16	60	170	29	167·7	33	33·7	0	50·8	41	83·1	41	182·0	47	53·0	47	95·2	63
17	65	112	13	110·0	38	20·3	0	27·4	11	62·3	61	127·3	49	30·1	24	76·9	78
18	70	120	24	151·2	41	35·5	0	38·2	39	77·5	60	151·2	55	33·6	44	82·1	83
19	63	160	30	157·1	37	39·2	0	48·3	25	69·6	65	160·6	46	49·3	33	72·0	80
20	69	115	18	162·6	23	44·5	0	49·8	20	68·1	40	194·8	40	53·5	33	96·6	62
21	62	105	28	168·7	38	48·3	0	50·3	34	70·1	68	181·8	49	51·2	44	82·2	81
22	100	125	41	180·7	27	79·0	0	38·4	17	63·2	67	—	—	—	—	—	—
Mean	74	136	21	146	42	25	0	35	27	86	58	161	56	37	41	102	74
± SD	13	23	9	32	9	18	0	15	12	19	9	35	9	15	8	24	7
Controls																	
23	79	144	14	104·6	61					104·6	61	114·3	72			114·3	72
24	90	100	14	65·2	57					65·2	57	73·7	77			73·3	77
25	67	140	6	109·1	64					109·1	64	115·3	76			115·3	76
26	71	140	7	106·8	67					106·8	67	116·2	81			116·2	81
27	81	128	9	87·4	59					87·4	59	103·0	68			103·0	68
28	99	128	5	84·2	57					84·2	57	83·5	71			83·5	71
29	67	105	12	103·1	61					103·1	61	—	—			—	—
30	62	160	14	110·4	64					110·4	64	122·7	77			122·7	77
31	60	120	10	110·5	66					110·5	66	—	—			—	—
Mean	75	129	10	98	62					98	62	104	75			104	75
± SD	13	19	4	15	4					15	4	19	4			19	4
P-vs. controls	NS	NS	< 0·001	< 0·001	< 0·001					NS	NS	< 0·001	< 0·001			NS	NS

SD, standard deviation; NS, not significant.

Ejection fraction of the total left ventricle was significantly lower in patients with aneurysm (42%) than in controls (62%, $P < 0{\cdot}001$). The transitional section showed a depressed ejection fraction of 27 per cent which was lower than the ejection fraction of the contractile section ($P < 0{\cdot}001$) but higher than that of the noncontractile section. The ejection fraction of the transitional section increased after premature beat from 27 to 41 per cent ($P < 0{\cdot}001$, Table). Volumes of the contractile section showed a wide scatter of data but the mean value was not significantly reduced in patients with aneurysms, and the ejection fraction was normal ($P > 0{\cdot}05$, Table). While heart rate and left ventricular systolic pressure were comparable in both groups ($P > 0{\cdot}05$, Table) the left ventricular end-diastolic pressure was significantly raised in patients with aneurysms as compared with controls (21 vs. 10 mmHg, $P < 0{\cdot}001$). After the premature beat, the ejection fraction for the total left ventricle was augmented in both groups but was again significantly lower in patients with aneurysm (56

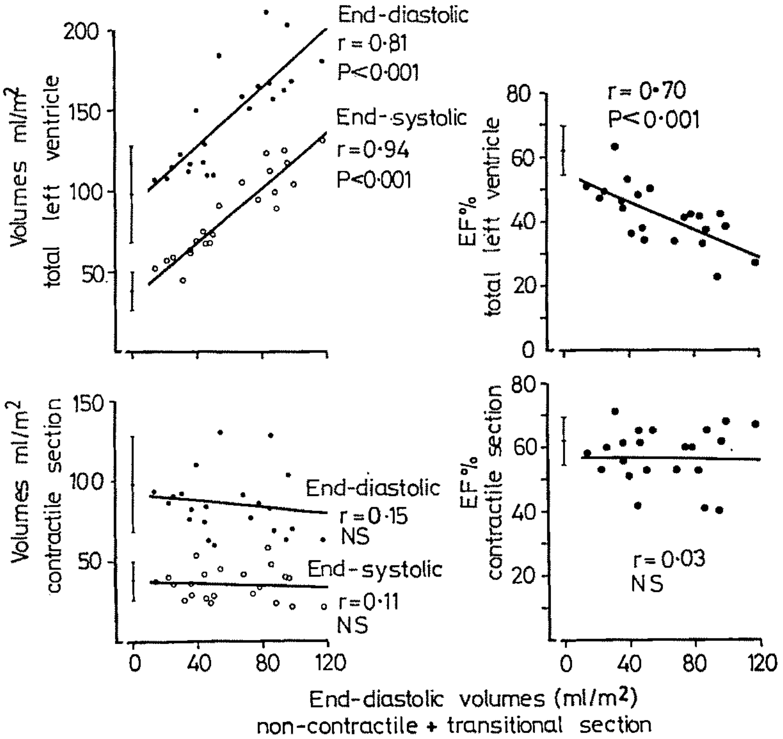


Fig. 3 *End-diastolic volumes of noncontractile + transitional section (aneurysmal size) show close relations to end-diastolic volume, end-systolic volume, and ejection fraction (EF) of total left ventricle (upper panels), but not to volumes and ejection fraction of contractile section (lower panels). The contractile section was perfused by normal coronary arteries.*

vs. 75%, P < 0·001, Table). The ejection fraction for the contractile section in patients with aneurysms was not different from total ejection fraction in controls (74 vs. 75%, P > 0·05). Fig. 3 represents the relation between end-diastolic volumes of noncontractile plus transitional sections and volumes and ejection fraction of total left ventricle (upper panels). Close relations were found for end-diastolic volume (r = 0·81, P < 0·001), end-systolic volume (r = 0·94, P < 0·001), and ejection fraction (r = 0·70, P < 0·001). The lower panels show no significant relations between end-diastolic volumes of the noncontractile plus transitional sections and end-diastolic volume (r = 0·15, P > 0·05), end-systolic volume (r = 0·11, P > 0·05), and ejection fraction (r = 0·03, P > 0·05) of the contractile section.

HISTOLOGICAL DATA

Light microscopy disclosed severe fibrosis mixed with only minimal myocardial tissue in the noncontractile section of the resected aneurysms in all patients studied (Fig. 4). The transitional section, however, contained various amounts of normally arranged myocardium mixed with fibrosis as shown in Fig. 5. The remaining myocardial tissue was found regularly in the subepicardial region, while the fibrosis was confined mainly to the subendocardium. As shown in Fig. 4 and 5, the noncontractile section was considerably thinner than the transitional section (identical magnification in both figures).

BEFORE AND AFTER ANEURYSMECTOMY

Six patients with large anterior aneurysms underwent aneurysmectomy without coronary bypass surgery. Aneurysmectomy was performed because of congestive heart failure in 5 patients and because of severe ventricular rhythm disturbances in 1 patient. Three of these patients had complete left anterior descending artery occlusion and only poorly visualised collaterals (evaluated according to Levin *et al.*, 1973). Three other patients had a 90 per cent obstruction of the left anterior descend-

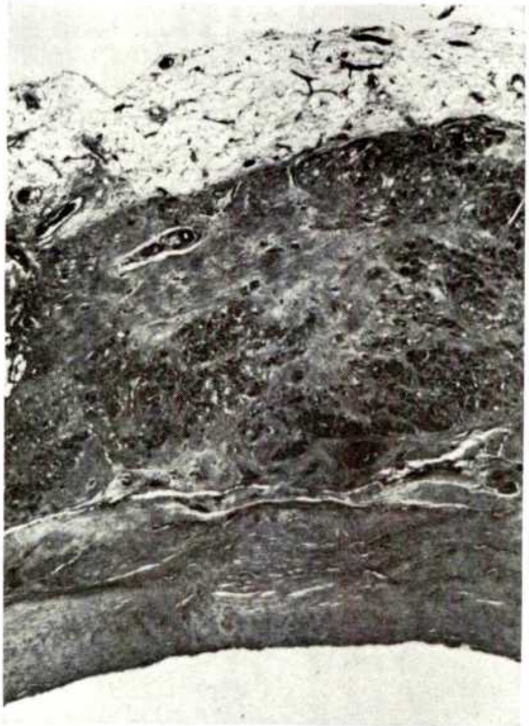


Fig. 4 *Light micrograph (cross-section) of the noncontractile section of an anterior aneurysm in a patient with obstructive disease of the anterior descending coronary artery. Severe transmural fibrosis between epicardial fat (upper margin) and endocardium (lower margin) is seen. (Haematoxylin-eosin. × 16.)*

ing artery with poor run-off. Poor collaterals were seen in only 1 of these 3 patients. When the volume of the noncontractile section was expressed as a percentage of total left ventricular end-diastolic volume the average in the surgical cases was 24·3 per cent (range 11 to 43%), which shows that large aneurysms were found in these patients. Patients were restudied between 6 and 10 months (8·1 ± 1·8 months) after operation. Heart rate (before = 82 ± 14 bpm, after = 79 ± 10 bpm) and left ventricular systolic pressure (before = 123 ± 20 mmHg, after 124 ± 10 mmHg) were comparable before and after operation. Left ventricular end-diastolic pressure (before = 23 ± 11 mmHg, after = 25 ± 11 mmHg) remained unchanged after operation. Individual data of volumes, ejection fraction, and end-diastolic pressure are shown in Fig. 6. End-diastolic volume declined significantly from 194 ± 29 to 133 ± 30 ml/m^2 ($P < 0{\cdot}001$), and end-systolic volume from 124 ± 14 to 83 ± 17 ml/m^2 ($P < 0{\cdot}001$). End-diastolic and end-systolic volumes

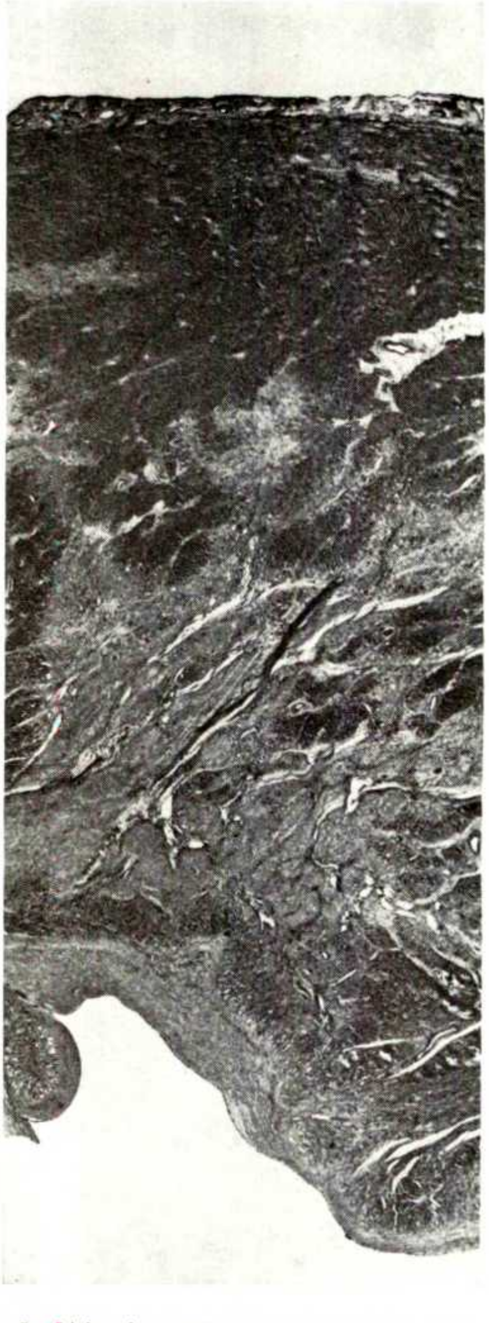


Fig. 5 *Light micrograph (cross-section) of the transitional section in the same patient shown in Fig. 4. Note normally arranged myocardium in the subepicardium and fibrosis in the subendocardium. The ventricular wall is thicker in the transitional section than in the noncontractile section of the aneurysm. (Haematoxylin-eosin. × 16.)*

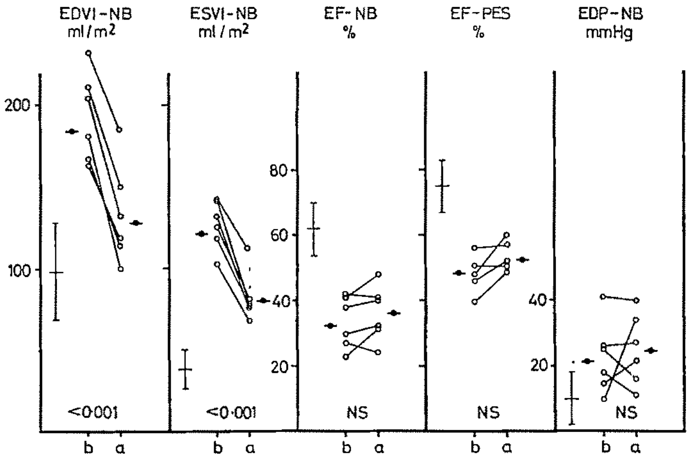


Fig. 6 *Haemodynamic data before* (b) *and after* (a) *aneurysmectomy. Normal range (mean value ± 2 standard deviation) is indicated by vertical lines. End-diastolic volumes and end-systolic volumes fell after surgery, but end-systolic volumes did not reach normal level. The ejection fractions (EF) and end-diastolic left ventricular pressure (EDP) remained unchanged. EDVI−NB = end-diastolic volume during normal beat; ESVI−NB = end-systolic volume during normal beat; EF−PES = EF after postextrasystolic beat; EDP−NB = end-diastolic left ventricular pressure during normal beat.*

were raised in patients after aneurysmectomy when compared with controls ($P < 0·05$). The absolute decrease of end-systolic volume index (41 ± 9 ml/m^2) was lower than the decrease in end-diastolic volume index (61 ± 13 ml/m^2) when comparing paired data ($P < 0·01$). There was no change in ejection fraction during normal or post-extrasystolic beats after operation ($P > 0·05$).

The average end-diastolic volume of the noncontractile section (46 ± 18·2 ml/m^2) and transitional section (50·2 ± 22·5 ml/m^2) in operated patients was compared with the volume of the aneurysm resected which was 64·2 ± 13·8 ml/m^2 (calculated as total preoperative end-diastolic volume minus total postoperative end-diastolic volume). Thus, the volume of the aneurysm resected exceeded the volume of the noncontractile section and excision must therefore have included part of the transitional section.

End-diastolic and end-systolic silhouettes of one patient's ventricle before and 6 months after operation are shown in Fig. 7. Before operation a large anterior aneurysm was present; after operation the end-diastolic silhouette was smaller but a large akinetic anterior segment was still found. This figure also depicts a system of 10 hemiaxes, which was used to calculate regional wall motion. Fig. 8 illustrates the percentage shortening of 10 hemiaxes for all patients before (upper panel) and after operation (middle panel) as compared with controls (lower panel) during normal and postextrasystolic beats. It is evident that before and after operation identical hemiaxes are akinetic ($R_2 - R_5$) while the inferior area perfused by normal coronary arteries shows normal regional wall motion. The hemiaxes R_6 and R_7 showed a significant increase in wall motion during normal beats after operation ($P < 0·05$ comparing paired data). After a premature beat no significant increase in regional wall motion was found ($P > 0·05$).

Discussion

Our series of patients with anterior aneurysm is not a consecutive series because patients with obstructive coronary lesions of the right coronary artery and the circumflex branch of the left coronary artery were excluded. Our patients therefore did not present with two coexisting problems, that is the mechanical disadvantage from the aneurysm and the functional impairment of the contractile section caused by additional coronary obstructions. Our technique for calculating the size of the aneurysm was derived from Kitamura *et al.* (1973). We modified their technique since we calculated total left ventricular volumes from biplane instead of monoplane cineangiograms. Validity of this technique is given by comparison of monoplane and

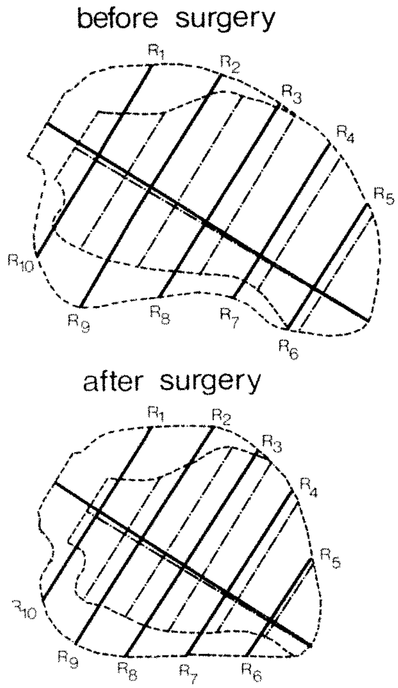


Fig. 7 *End-diastolic and end-systolic silhouettes of a ventricle before and after aneurysmectomy. After surgery the ventricular chamber is smaller but a large akinetic area persists.* R_1*-*R_{10} *are hemiaxes which are drawn to measure regional wall motion.*

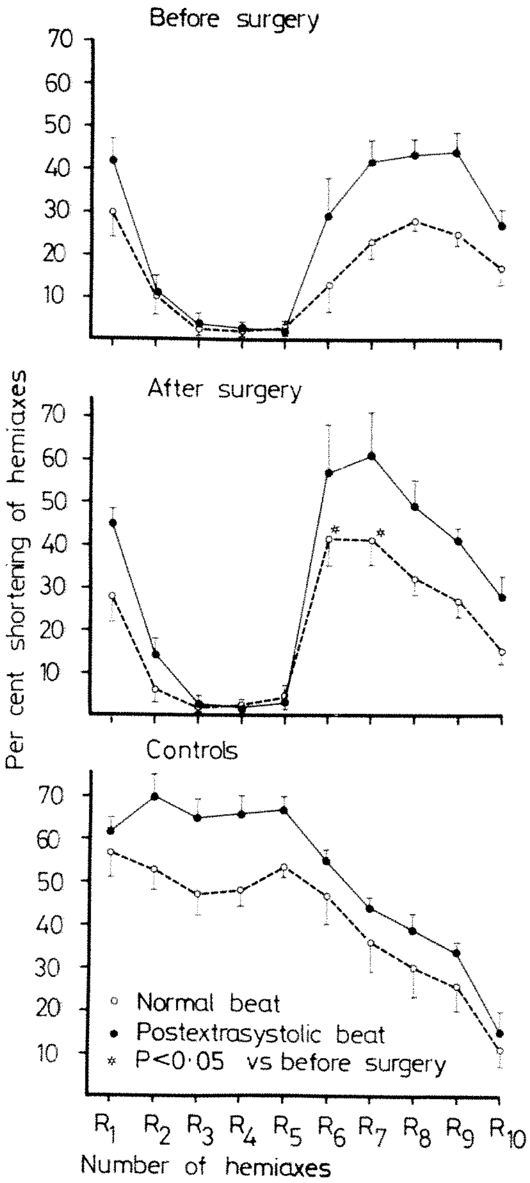


Fig. 8 *Percentage shortening of hemiaxes is shown for anterior aneurysms before and after aneurysmectomy as compared with controls. A lack of motion is seen before and after surgery for* R_2*-*R_5*, hypokinesia for* R_1*. A significantly improved wall motion of* R_6 *and* R_7 *after surgery is evident during normal beats but not during postextrasystolic beats. Interrupted line and open circles = normal beat; uninterrupted line and closed circles = postextrasystolic beat.*

biplane volumes as shown in Fig. 2. In addition, a border zone (transitional section) was defined as a section with severely depressed but not absent motion. We defined this section in the postextrasystolic beat, since it is well known that inotropic stimulation enhances motion in areas partially fibrotic (Dyke *et al.*, 1974). Our decision seems justified from the histological studies: while the noncontractile section in all patients consisted of fibrosis without myocardium, the transitional section contained considerable amounts of viable myocardium mixed with scar tissue, which explains the transitional section ejection fraction of 27 per cent and the increase after premature beat to 41 per cent. The transitional section most probably represents the border-zone between fibrotic tissue and an area which was ischaemic during acute coronary artery occlusion, but was partially preserved by the development of collaterals (Snow *et al.*, 1955; Schaper, 1971). This hypothesis is further supported by the fact that in 4 of 6 operated patients collaterals were visible before operation. The evolution and distribution of collateral flow during acute myocardial infarction was measured in dogs by the tracer microsphere technique and normalisation of flow in ischaemic marginal areas and the subepicardium of central areas was found after 24 to 48 hours (Cox *et al.*, 1975; Pasyk and Schaper, 1975).

When the aneurysmal volume was defined as non-contractile plus transitional section, then the contractile section showed a normal contractile behaviour which did not deteriorate with increasing size of aneurysm. Watson *et al.* (1975) described a wide range of contractile section ejection fractions in ventricular aneurysms; however, in their study 14 of 17 patients had severe obstructive lesions of more than one coronary artery. Our findings are only applicable to a normally perfused contractile section. The relation between size of aneurysm and total ejection fraction (Fig. 3) signifies declining function with increasing aneurysmal size. This relation confirms the results described by Feild *et al.* (1972) and Kitamura *et al.* (1973). The normal function and reserve in the contractile section of our patients signifies that the increased systolic load produced by an increased ventricular volume plays no significant role for systolic function of the non-infarcted normal myocardium in patients with aneurysm. From the theoretical point of view, aneurysmectomy should reduce end-diastolic and end-systolic volumes by about the same amount, and the ejection fraction should increase. We have studied 6 patients with anterior aneurysm and isolated disease of the left anterior descending branch of left coronary artery. The decrease of end-systolic volume was found to be significantly less than that of end-diastolic volume, and the ejection fraction remained unchanged. The lack of improvement was further reflected by an unchanged left ventricular end-diastolic pressure. This fact could be the result of insufficient resection of the aneurysm. However, the aneurysms were resected to the transitional section according to the technique of Favaloro *et al.* (1968) leaving a rim of scar tissue for support of the sutures. On the other hand, the sutures in the transitional section may destroy its contractile behaviour. This latter mechanism is suggested by the wall motion pattern shown in Fig. 7 and 8: a large akinetic area after operation persisted. Studies comparing ventricular function by cineangiography before and after aneurysmectomy are rare. Kitamura *et al.* (1972) reported a series of 9 patients who underwent aneurysmectomy associated with aortocoronary bypass surgery in 4 patients and internal mammary implants in the remaining 5 patients. The ejection fraction in their series improved from 31 to 44 per cent but remained severely depressed after surgery. In an experimental study in dogs, Pairolero *et al.* (1970) found no improvement in left ventricular function after excision of a large chronic infarct as measured by the percentage shortening of the angiographic ventricular silhouette and by construction of ventricular function curves. Our study suggests that aneurysmectomy does not significantly improve cardiac function and cardiac reserve, probably because the reduction in end-diastolic and end-systolic volume is partially jeopardised by the fact that transitional section becomes akinetic after the surgical procedure. Further investigation is needed to clarify if a more limited resection (removing the thinned scar only) associated with aortocoronary bypass surgery (revascularising the transitional section) may improve ventricular function in patients with ventricular aneurysm.

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Electrophysiological effects of L 9394 (benzoyl-indolizine) in man

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SUMMARY The electrophysiological effects of L 9394 (benzoyl-indolizine), a substance chemically related to amiodarone, but devoid of iodine atoms, were investigated by programmed electrical stimulation of the heart in 12 patients with various forms of tachycardia. Four subjects had electrocardiographic evidence of the WPW syndrome and episodes of circus movement tachycardia. Paroxysmal supraventricular tachycardia, confined to the atrioventricular (AV) node, was found in 3 patients. In 2 cases, where a short PR interval was present, the main complaint was the occurrence of paroxysmal atrial fibrillation. In the remaining 3 instances, the arrhythmia consisted of slow ventricular tachycardia (1 case), supraventricular tachycardia of the focal type (1 case), and episodes of primary ventricular fibrillation, not related to acute myocardial ischaemia (1 case).

L 9394 injected intravenously was seen to lengthen the transnodal conduction time as well as the effective and functional refractory periods of the node. Similar effects were found on the retrograde VA pathway. The drug had no action on the infra-Hisian conduction system, on the refractory periods of ventricular muscle, or on the refractory periods of accessory bypasses.

The drug was injected during an episode of tachycardia in 6 cases with reproducible supraventricular re-entrant tachycardia. Three had a tachycardia circuit confined to the node. In those instances, the drug had beneficial effects (slowing and interruption of tachycardia, decrease or abolition of echo zone; loss of ability to induce tachycardia). In the other 3 cases, an accessory pathway was incorporated in the circuit. L 9394 interrupted the tachycardia in 2 instances (by anterograde AV block), but failed to protect all 3 patients against reinitiation of tachycardia by premature stimuli.

It is concluded that L 9394 does not share all the pharmacological properties of amiodarone and will not replace it in all its indications.

Amiodarone has been reported to be an effective antiarrhythmic agent for different types of arrhythmia (Coumel *et al.*, 1974; Rosenbaum *et al.*, 1974; Touboul *et al.*, 1975; Rosenbaum *et al.*, 1976; Wellens *et al.*, 1976; Waleffe *et al.*, 1978). Side-effects however have limited wide acceptance of the drug in clinical practice (Geerts, 1971; Verin *et al.*, 1971; Babel and Stangos, 1973; Pritchard *et al.*, 1975; Burger *et al.*, 1976). L 9394, a benzoyl-indolizine derivative, is a new substance which is chemically related to amiodarone (Fig. 1) (Charlier *et al.*, 1976, 1977). However, since L 9394 is not a carrier of iodine atoms, there are reasons to believe that the drug is likely to be devoid of at least some of the side-effects of amiodarone. We therefore decided to investigate the electrophysiological properties of L 9394 in man.

Subjects and methods

Twelve patients were studied. Data on age, sex, and type of arrhythmia are given in Table 1.

After obtaining informed consent, 4 catheters were introduced into the femoral vein using the Seldinger technique. One quadripolar catheter was positioned high on the lateral wall of the right atrium: the two distal electrodes were used for stimulation and the proximal electrodes for re-

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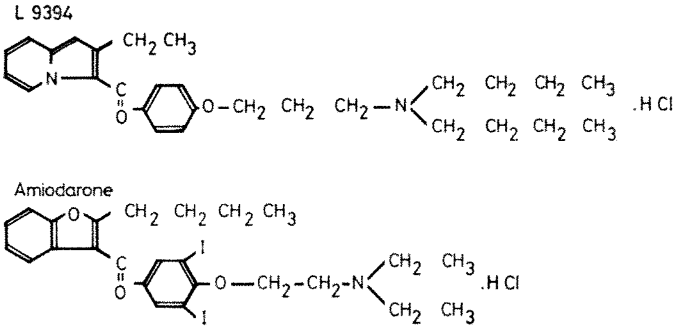

Fig. 1 *Chemical structure of L 9394 as compared with amiodarone.*

Table 1 *Clinical features*

Case no.	*Age and sex*		*Diagnosis*
1	20	F	AVN RT
2	23	F	AVN RT
3	38	F	AVN RT
4	55	M	Short PR + AF
5	27	F	Intermittent WPW type A + CMT
6	34	F	WPW type B + CMT
7	26	M	WPW type A + CMT + AF
8	51	M	WPW type B
9	18	M	Short PR + AF
10	19	M	Slow VT
11	56	F	VF
12	22	M	SVT (focal type)

AF, atrial fibrillation; AVN RT, AV nodal re-entrant tachycardia; CMT, circus movement tachycardia; VF, ventricular fibrillation; VT, ventricular tachycardia; SVT, supraventricular tachycardia; WPW, Wolff-Parkinson-White syndrome.

cording the intra-atrial electrogram. A bipolar catheter was placed close to the bundle of His to record the His bundle electrogram. The third (bipolar) catheter was positioned in the apex of the right ventricle and was used for ventricular stimulation.

In 6 patients, in order to record a left atrial electrogram, a fourth quadripolar catheter was advanced into the coronary sinus or, through a patent foramen ovale, into the left atrial cavity.

Using the extrastimulus technique, the effective refractory period of the right atrium, the effective and functional refractory periods of the AV node, and the effective refractory period of the right ventricle and of the accessory pathway, when present, were measured. The zones of premature beat intervals resulting in atrial echoes or sustained tachycardia were carefully determined. The right ventricle was paced up to its effective refractory period. The pattern and refractory period of VA conduction were registered. Atrial and ventricular pacing were first done at rates slightly above the spontaneous rate, and thereafter at shorter cycle lengths.

Table 2 *Effects of L 9394 on electrophysiological indices: comparison of control values with longest values observed after drug administration*

Case no.	*Pacing cycle length (ms)*	*AH interval (ms)*			*HV interval (ms)*		*ERP$_{RA}$ (ms)*			*AV node (AV direction) ERP (ms)*		
		Before	*After*	△	*Before*	*After*	*Before*	*After*	△	*Before*	*After*	△
1	500	120	120	0	30	50	—	—	—	220	300	[illegible]
2	550 500	50	60	10	35	35	215	235	20	< 225	360	> 1
3	470	70	100	30	40	40	210	230	20	< 230	330	> 1
4	600	50	70	20	20	20	210	225	15	< 235	340	> 1
5	470	100	115	15	30*	30*	175	215	40	< 200	420	2
6	500	80	85	5	30†	30†	195	210	15	240	> 280	>
7	600	100	?	?	− 40	?	250	270	20	?	?	?
8	550	?	?	?	50*	?	210	210	0	< 240	> 310	>
9	500	110	120/240	10/130	30	30	240	280	40	250	380	1
10	500 550	110	140	30	30	30	170	190	20	230	330	1
11	600	120	170	50	40	40	230	250	20	< 250	420	> 1
12	500 600	90	120	30	40	40	190	190	0	280	380	1
Mean difference				+32					+19·10			> 1
P				< 0·05					< 0·001			< 0

ERP, effective refractory period; FRP, functional refractory period; RA, right atrium; RV, right ventricle; AP, accessory pathway. *Without pre-excitation; †During circus movement tachycardia.

The various measurements were made before and after the injection of 2 mg/kg of L 9394, administered intravenously over a 5-minute period. All measurements were repeated at the end of the injection (time zero) and again every fifteenth minute, during 1 hour.

All data obtained during the stimulation study were recorded on tape (HP 8868 A) and directly registered on an eight-channel Elema Mingograf recorder. Leads I, II, III, V1, V6, the intracavitary right atrial lead, the left atrial lead (when available), and the His bundle electrogram were simultaneously recorded. For recording the His bundle electrogram, a 854 Universal Amplifier with input adapter was used.

The effective refractory period of the AV node was defined as the longest A_1-A_2 interval failing to conduct through the AV node. The functional refractory period (FRP) of the AV node was considered as the shortest H_1-H_2 interval that could be obtained. Since it was not always possible to determine when the AV node became refractory during ventricular pacing (because of absence of a retrograde H potential and/or because of a gap phenomenon in VA conduction), no values will be given for the effective refractory period of the different parts of the VA conduction system. Statistical analysis was performed using the paired t test. Plasma levels of L 9394 were determined by using a chromatographic method (J. Broekhuysen, 1977, personal communication).

Results

The results are summarised in Table 2.

AV CONDUCTION

As indicated in the Table, the AH interval lengthened after the L 9394 injection in all but 1 of the 10 patients in whom it could be measured. Mean increase in AH interval was 32 ms (range 0 to 130 ms) ($P < 0.05$). In case 9, a sudden and distinct lengthening of the AH interval (jump from 120 to 240 ms) was transiently observed 30 minutes after the administration of L 9394.

Because some patients had the WPW syndrome, the refractory periods of the AV node could not be measured in all studies. The effective refractory period measured in 11 patients increased by an average of more than 113·6 ms ($P < 0.001$). The functional refractory period increased by an average of more than 89·4 ms ($P < 0.001$).

A pattern suggestive of a dual AV nodal pathway was present before L 9394 administration in 2 patients (cases 1 and 9). L 9394 did not alter the broken aspect of the AV conduction curve in case 9, the electrophysiological properties of both pathways being similarly affected by the drug. But in case 1, a smooth curve was observed during the initial 20 minutes after drug injection. In 2 patients (cases 3 and 5), the injection of L 9394 revealed a dual AV nodal pathway curve that had not been depicted before drug administration. In case 5, this dual pathway curve appeared 20 minutes after injection and persisted until the end of the investigation. In case 2, a patient with AV nodal re-entrant tachycardia, a smooth AV conduction curve was consistently obtained both before and after the administration of L 9394.

In patients without pre-excitation no change was observed in the HV interval.

(ms)			*VA conduction system ERP (ms)*			ERP_{HV} *(ms)*			ERP_{AP} *(ms) AV direction*			*VA direction*		
re	*After*	△	*Before*	*After*	△	*Before*	*After*	△	*Before*	*After*	△	*Before*	*After*	△
	420	80	240	410	170	220	230	10						
	> 360	> 10	≤220	300	> 80	200	210	10						
	> 410	> 90	≤230	≤230	? 0	220	220	0						
	450	50	≤275	≤270	?	265	255	− 10						
	430	105	?	?	?	215	225	10	440	?	?	< 225	< 240	?
	?	?	?	?	?	240	230	− 10	280	280	0	280	290	10
	?	?	?	?	?	230	220	− 10	< 270	< 290	?	< 240	260	> 20
	?	?	< 260	< 260	?	240	240	0	290	310	20	340	350	10
	540	100	< 230	410	> 180	210	210	0						
	460	100												
			270	410	140	200	210	10						
	530	170	290	block	∞	280	290	10						
	440	100												
			360	500	140	330	220	− 110						
		> 89·4 < 0·001			> 142 < 0·01			− 7·5 NS			NS			> 13·3 NS

Table 3 *Effects of L 9394 on tachycardia*

Case no.	*CL*	*Tachycardia type*	*Initiation*		*Tachycardia zone (ms)*		*RR interval during tachycardia (ms)*	
			Before	*After*	*Before*	*After*	*Before*	*After*
1	500	AVN RT	1 APB	—	250-230	—	360	—
	500	AF	1 APB	—	210-180		400	—
2	300	AVN RT	Rapid atrial pacing	—			330	—
	300		Rapid ventricular pacing	—			330	—
3	SR	AVN RT	2 APB 3 APB	—			310	—
	270		rapid atrial pacing	—				
5	470	CMT (WPW)	2 APB	1 APB		320-265	290-380	450
	470		3 VPB	1 VPB		390-300		
	290		rapid atrial pacing	—				
6	500	CMT (WPW)	1 APB	—	280-255	—	300	390
	500		—	1 VPB	—	290		
7	600	CMT (WPW)	1 VPB	1 VPB	310-300	350	320-360	450

CL, cycle length; AVN RT, AV nodal re-entrant tachycardia; AF, atrial flutter; CMT, circus movement tachycardia; APB, atrial premature beat; VPB, ventricular premature beat; SR, sinus rhythm.

VA CONDUCTION

In 3 patients (cases 5, 6, 7), the presence of an accessory pathway (with an effective refractory period in VA direction shorter than that of the ventriculoatrial conducting system) did not permit accurate evaluation of changes in VA conduction characteristics through the His AV nodal axis.

In 3 patients (cases 3, 4, 8), VA conduction persisted after drug administration up to the functional refractory period of the ventricle.

In 1 patient, after L 9394, a complete VA block occurred (case 11). Finally, in the remaining 5

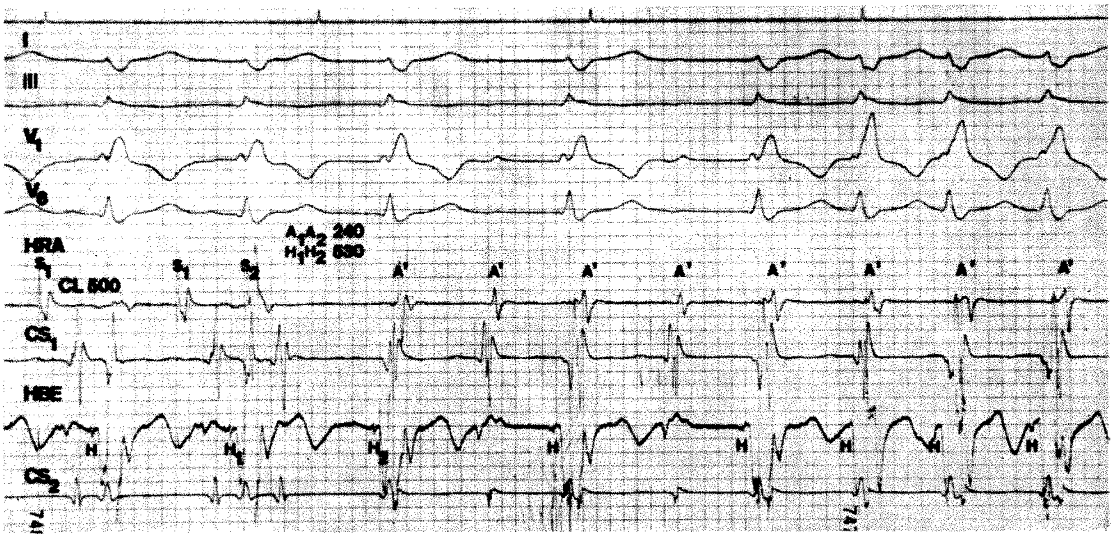

Fig. 2(a)

Fig. 2 *Case 1. Eight leads are simultaneously recorded: I, III, V1, V6, HRA (high right atrial lead), CS_1 and CS_2 (two coronary sinus leads), and the HBE (His bundle electrogram).*
In (a) *before drug administration, at a A_1A_2 interval of 240 ms, a long AH interval is observed (H_1H_2 = 530 ms) and an episode of AV nodal re-entrant tachycardia (with transient 2:1 AV block) is initiated.*
In (b) *and* (c) *after administration of L 9394, a jump in the curve plotting the H_1H_2 intervals against the A_1A_2 intervals is still observed (H_1H_2 equals 410 ms for an A_1A_2 of 350 ms, and 550 ms for an A_1A_2 of 340 ms). In spite of this, no echo beat or tachycardia is elicited, the fast conducting pathway being now blocked in the retrograde direction.*

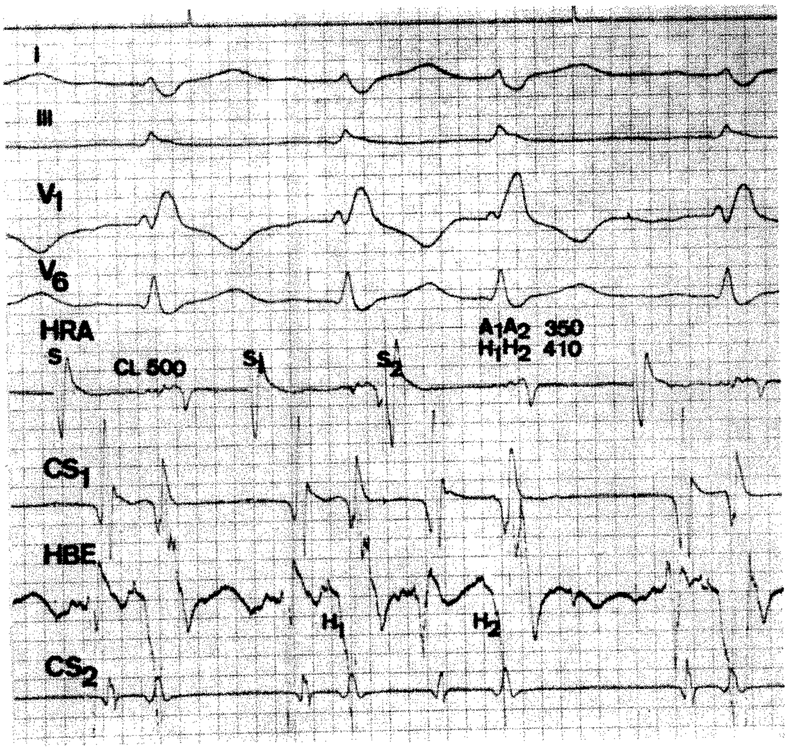
I
III
V1
V6
HRA
S
CL 500
S1
S2
A1A2 350
H1H2 410
CS1
HBE
H1
H2
CS2

Fig. 2(b)

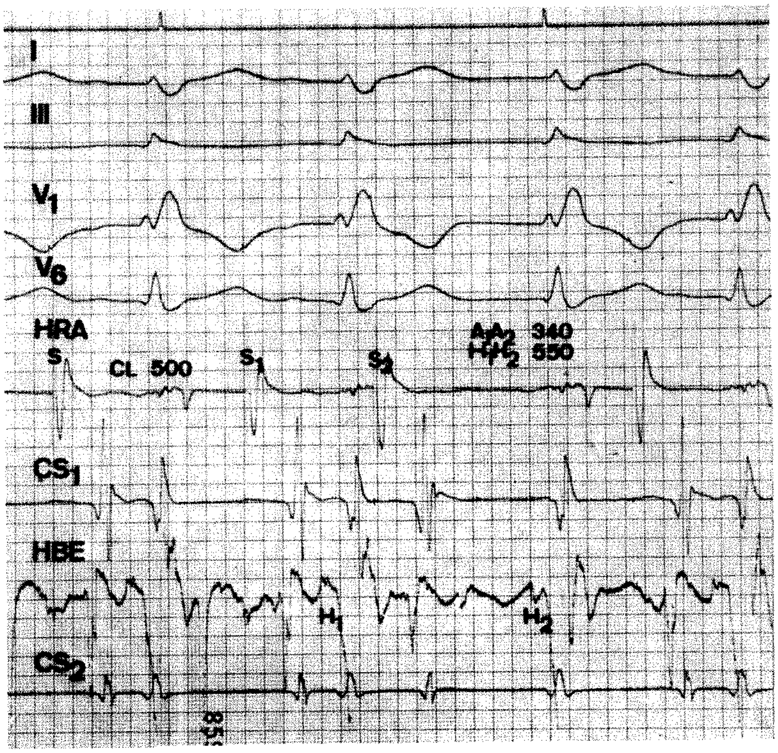
I
III
V1
V6
HRA
S
CL 500
S1
S2
A1A2 340
H1H2 550
CS1
HBE
H1
H2
CS2

Fig. 2(c)

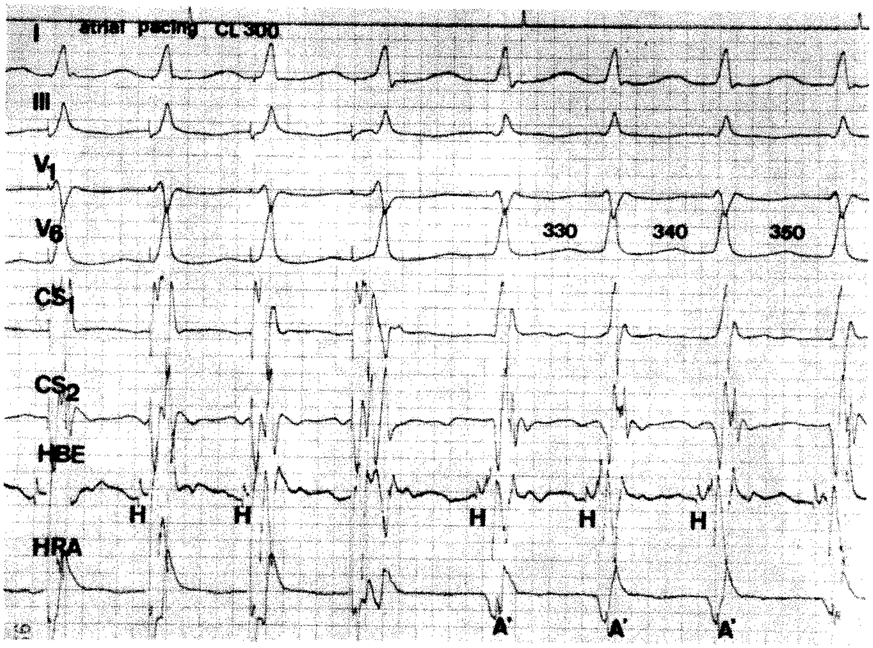

Fig. 3(a)

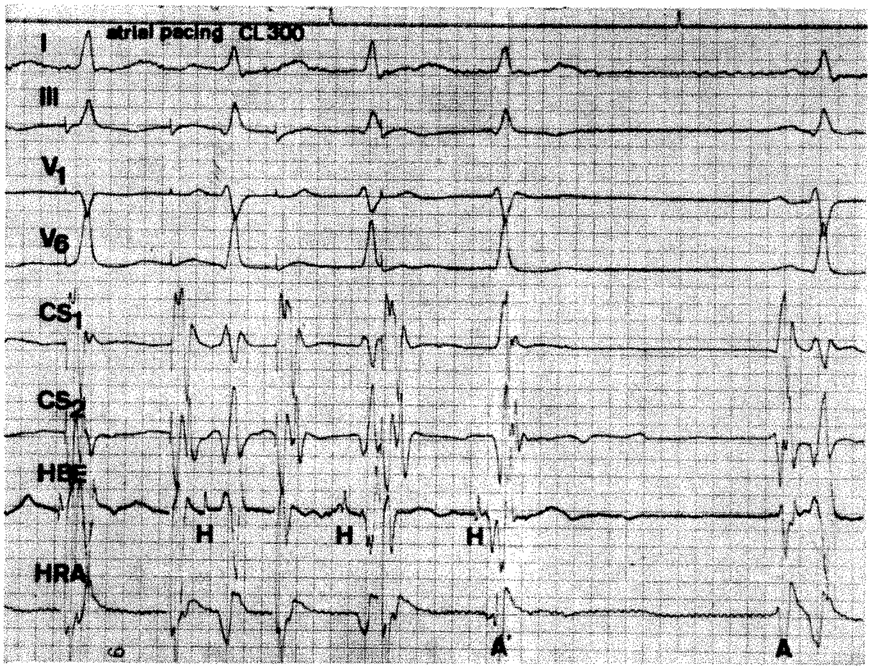

Fig. 3(b)

Fig. 3 *Case 2.* (a) *Before drug administration, atrial pacing at a cycle length of 300 ms results in a Wenckebach type of response and its interruption is followed by the initiation of an episode of tachycardia (AV nodal re-entrant tachycardia).* (b) *After administration of L 9394, the Wenckebach type of block is more obvious during atrial pacing. After interruption of pacing, one AV nodal re-entry cycle is completed, but this is not followed by tachycardia, the slow conducting pathway being now blocked in the anterograde direction.*

subjects (cases 1, 2, 9, 10, 12), the effective refractory period of the VA conduction system lengthened by an average of at least 142 ms.

EFFECTIVE REFRACTORY PERIOD OF RA AND RV

In all but 2 cases, the ERP of the right atrium slightly lengthened. The changes were statistically significant ($P < 0{\cdot}001$) but, in absolute values, they appeared trivial. The ERP of the right ventricle failed to show any consistent alteration.

ERP OF ACCESSORY PATHWAY

An accessory pathway was present in 4 cases (2 right-sided; 2 left-sided). The drug was found to have no effect on its effective refractory period either in anterograde or retrograde direction.

MECHANISM OF TACHYCARDIA

In the 3 patients with AV nodal re-entrant tachycardia (cases 1 to 3), and in 3 of the 4 subjects with WPW (cases 5 to 7), episodes of tachycardia could be initiated by electrical stimulation (Table 3).

In case 1 (Fig. 2), before the administration of the drug, a single atrial extrastimulus (S_2) delivered between 250 and 230 ms after the preceding stimulus (S_1) initiated an AV nodal re-entrant tachycardia with a cycle length of 360 ms. In addition, S_2 stimuli, delivered from 210 ms to 180 ms after S_1, started episodes of atrial flutter with a ventricular cycle length of 400 ms. After L 9394 administration, the jump in the curve plotting the H_1H_2 against the A_1A_2 intervals transiently disappeared; it was again observed after a 20-minute period; extrastimuli however could induce only one or two re-entrant echo beats, but no sustained tachycardia. Atrial flutter could not be elicited.

In case 2, AV nodal re-entrant tachycardia could be started only by rapid atrial or ventricular pacing (Fig. 3). After L 9394, no tachycardia could be induced.

In case 3, supraventricular tachycardia could be initiated by 2 or 3 atrial extrastimuli or by rapid atrial pacing. After drug administration, the ability to induce tachycardia was lost in spite of the unmasking effect of a previously concealed dual AV nodal pathway.

In case 5 (Fig. 4), a left-sided accessory pathway was associated with a dual AV nodal pathway curve unmasked by L 9394 injection. Episodes of tachycardia with two different cardiac rates (suggesting circuits with AV conduction over either the fast, or the slow AV nodal pathway, and VA conduction over the accessory pathway) could be initiated before drug administration by giving a salvo of at least 3 ventricular extrastimuli, more rarely by 2 atrial premature beats, or by rapid atrial pacing at a rate producing a Wenckebach phenomenon. After the drug, a jump in the AV conduction curve became clearly apparent. Initiation and termination of tachycardia were facilitated. Circus movement tachycardia, using the accessory pathway retrogradely, could be started by either a single ventricular or atrial premature beat with relatively large tachycardia zones (at that time the fast AV nodal pathway had become refractory), by rapid atrial pacing at rates producing a second degree AV block, and by ventricular pacing. The tachycardia could easily be terminated by 2 ventricular premature beats and, with greater difficulty, by a single ventricular extrastimulus, or by 3 atrial premature beats. The tachycardia cycle length was significantly prolonged after L 9394 (410 ms as compared with 290 or 380 before the injection), this lengthening being in part the result of the exclusive use of the slow AV nodal pathway for anterograde conduction.

In 6 patients with reproducible paroxysmal re-entrant tachycardias, L 9394 was administered during an episode of tachycardia. The injection resulted in termination of the rhythm disorder in all patients with the intranodal type of tachycardia and in 2 of the 3 cases with the WPW syndrome (cases 5 and 7). The heart rate during tachycardia decreased in each subject; this was related to slowing of conduction along the AV node and not to prolongation of the VA conduction time.

OTHER INDICES

Sinus node function tests were not performed during this investigation because of a lack of time during the procedure.

In 2 of the cases, the threshold for atrial stimulation was noted to increase after L 9394 administration. In case 9, for example, the threshold at the end of injection rose to 20 mA. This value was 5 times greater than the control value. It fell to 7 mA 22 minutes later and to 5 mA after 30 minutes. In case 2, the threshold was measured at 7 mA at the end of the injection and at 4 mA 30 minutes later.

In the remaining subjects, no attempt was made to measure systematically the threshold for atrial stimulation. Since stimulation was done at twice the threshold value, any increase of less than 100 per cent would have passed unnoticed.

Arterial blood pressure was monitored throughout the study, in 4 cases by continuous intra-arterial pressure recording, and in the remaining instances by repeated measurements by sphygmomanometer. No significant change was observed.

The plasma level of L 9394 was 3·0 ng/ml ± 2·0 at the end of injection and 0·47 ± 0·21 15 minutes later. After the end of injection, the plasma levels showed an exponential decrease. No correlation was observed between the pharmacological effects and the plasma levels of the drug during this initial distribution period (Wellens and Durrer, 1974).

Discussion

The results of our investigation show that L 9394 is a substance which acts mainly on the AV node. It lengthens the transnodal conduction time as well as the effective and functional refractory periods of the node. As opposed to amiodarone (Touboul *et al.*, 1975; Wellens *et al.*, 1976; Waleffe *et al.*, 1978), it has no effect on anterograde conduction over the intraventricular conduction system, on ventricular muscle, and accessory pathways.

The observed changes are of the same order of magnitude as those which have been reported previously with ouabain (Wellens *et al.*, 1975; Wu *et al.*, 1975), propranolol (Wu *et al.*, 1974), and verapamil (Wellens *et al.*, 1977).

In contrast to verapamil (Wellens *et al.*, 1977), L 9394 had some effect on the retrograde VA pathway in several patients. This may of course reflect an action on the AV node but functional changes within the His-Purkinje system used retrogradely cannot be ruled out.

Our observations indicate that L 9394 is a potentially interesting drug for the treatment of tachycardias confined to the AV node. In the 3 patients whom we studied, the episodes of tachycardia were ended by the intravenous injection of the drug. In addition, L 9394 decreased or totally eliminated the echo zones and made the patients lose their ability to develop sustained paroxysmal supraventricular tachycardia during programmed electrical stimulation.

The effects in patients with circus movement tachycardia associated with pre-excitation are less clear. In the 3 patients studied, the drug produced slowing of transmission through the anterograde AV nodal part of the tachycardia circuit which resulted in a significant slowing of the cardiac rate during circus movement tachycardia. L 9394 interrupted tachycardia in 2 instances, but failed to protect all 3 patients against reinitiation of tachycardia by premature stimuli. These observations resemble those made in patients with concealed bypasses after administration of ouabain (Wellens *et al.*, 1975; Wu *et al.*, 1975), propranolol (Wu *et al.*, 1974), and verapamil (Wellens *et al.*, 1977). As pointed out by others (Wellens *et al.*, 1975; Wu *et al.*, 1975), by producing selective slowing of conduction within the AV node, these drugs, like L 9394, may actually favour the initiation and perpetuation of circus movement tachycardia in the presence of a ventriculoatrial accessory pathway. Delaying conduction through the node increases the chance for a premature impulse to reach the ventricular end of the bypass when it is excitable and thus promotes VA conduction over this pathway and initiation as well as perpetuation of tachycardia. This was clearly shown in case 5 of this series in whom an accessory bypass as well as a dual nodal pathway were simultaneously present. Prolongation of the conduction time especially along the slow nodal pathway made it much easier to induce the tachycardia after drug administration.

Drug induced changes of the pattern of atrioventricular conduction have previously been re-

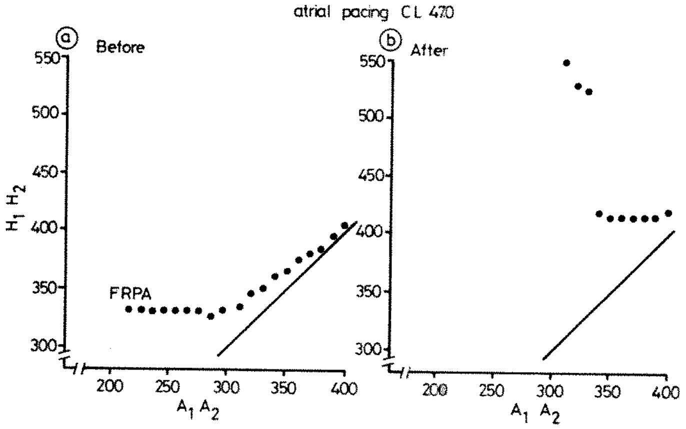

Fig. 4(a)

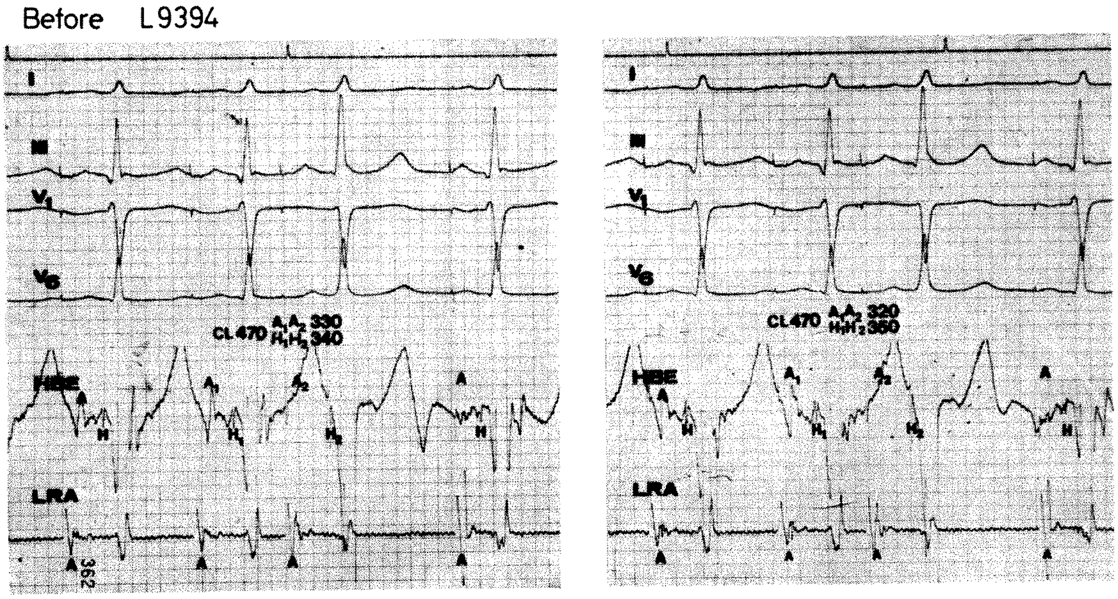

Fig. 4(b)

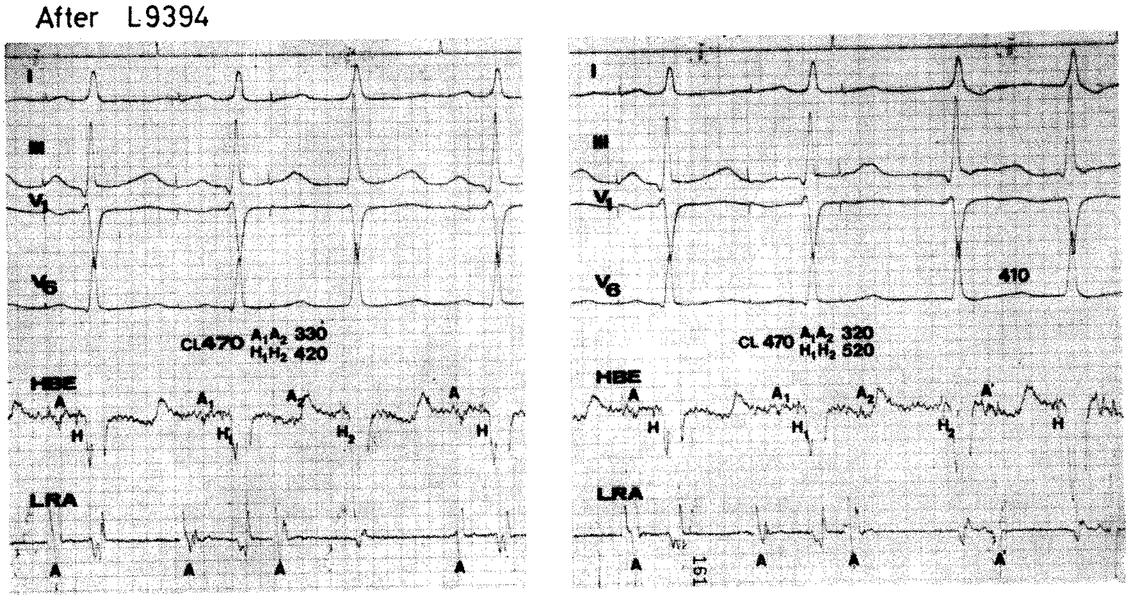

Fig. 4(c)

Fig. 4 *Case 5.* (a) *The curve plotting the H_1H_2 against the A_1A_2 intervals is smooth in the control state, but shows after administration of L 9394 a typical jump at 320 ms. Tracings were obtained before* (b) *and after* (c) *administration of the drug. Before L9394 (b) single ectopic beats elicited at A_1A_2 intervals of 330 and 320 ms failed to initiate tachycardia. After L9394* (c) *the ectopic beat elicited at an A_1A_2 interval of 320 ms produced a sudden increase of the AH time and initiated an episode of tachycardia with a longer cycle length (410 ms) than in the basic conditions (290 to 380 ms). LRA: low right atrial lead.*

ported (Wu *et al.*, 1974; Wellens *et al.*, 1975, 1977). Two different situations were encountered in this series. In 2 patients, a dual AV nodal pathway was shown only after administration of L 9394. In one other case, a dual pathway curve was identified before drug administration, but changed into a smooth curve afterwards. The possible explanations for such a phenomenon have been discussed previously (Wellens *et al.*, 1975).

In summary, it is apparent that L 9394 does not share all the pharmacological properties of amiodarone and in spite of its possibly better tolerance, it will not completely replace amiodarone. As it has little effect on the atrial and ventricular muscles and on the accessory pathways it is unlikely that L 9394 will be as effective as amiodarone on a large spectrum of arrhythmias. We want to stress however that our data were obtained after intravenous administration of L 9394. Little is known of the pharmacokinetics of this substance in the human. In addition, previous experience has indicated that the effect of intravenous amiodarone is different from that obtained after long-term oral administration (Berkman *et al.*, 1975). In view of this, chronic studies (Wu *et al.*, 1977) on the effect of L 9394 administered orally are needed before any definite conclusion can be drawn regarding the clinical usefulness of this drug.

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Effects of propranolol and metoprolol on haemodynamic and respiratory indices and on perceived exertion during exercise in hypertensive patients

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SUMMARY A double blind cross-over trial of the non-selective beta-blocker propranolol and the beta$_1$-selective blocker metoprolol was carried out in 8 hypertensive patients. At the end of each 4-week period of treatment haemodynamic and respiratory indices and perceived exertion were studied during moderate exercise. Both beta-blockers resulted in reduced heart rate, cardiac output, and blood pressure, whereas the stroke volume increased. Total peripheral resistance did not change. During exercise the expiratory peak flow rate equally increased in every period. However, the peak flow rate at rest, as well as during exercise, was reduced by propranolol, while metoprolol had no such influence. Neither of the beta-blockers changed O_2 consumption, CO_2 production, tidal volume, or respiratory rate. Moreover, they did not influence perceived exertion. These results suggest that the arteriolar and bronchiolar beta$_2$-receptors do not play a major role in the alteration of circulation and ventilation during exercise. As far as their practical use as antihypertensive agents is concerned, this study shows no advantage in the use of either of these beta-blockers.

During muscular exercise the plasma catecholamine concentration increases as a result of the increased activity of the sympathetic nervous system and the adrenal medulla (Vendsalu, 1960; Davies *et al.*, 1974; Galbo *et al.*, 1975). This increased adrenergic activity plays an important role in the adaptation of the circulatory system to exercise (Bevegård and Shephard, 1967). Adrenergic effects are mediated by stimulation of different kinds of receptors, which were nominated alpha- and beta-receptors by Ahlquist in 1948. Later the beta-receptors were divided by Lands *et al.* (1967) into two subgroups: beta$_1$ for the cardiac receptors and beta$_2$ for the arteriolar and bronchiolar receptors.

The beta$_1$-selective blockers, as well as the non-selective beta-blockers, reduce the heart rate, the cardiac output, and the blood pressure during exercise (Cumming and Carr, 1967; Johnsson *et al.*, 1969; Ablåd *et al.*, 1976; Reybrouck *et al.*, 1977). It is possible, however, that the haemodynamic changes induced by beta$_1$-selective and non-selective beta-blockers differ during exercise. For example, a non-selective beta-blocker, such as propranolol, could be expected to diminish the vasodilatation in exercising muscle by blockading the arteriolar beta$_2$-receptors. This would then affect the blood pressure. On the other hand, a much smaller effect on the peripheral resistance would be expected from a beta$_1$-selective blocker such as metoprolol (Johnsson, 1975; van Herwaarden *et al.*, 1977).

Moreover, it might be possible for a non-selective beta-blocker to partly inhibit the bronchodilatation that appears during exercise, by blockading the bronchiolar beta$_2$-receptors. On the other hand, a beta$_1$-selective blocker would not hinder this bronchodilatation (Johnsson *et al.*, 1975b; Tivenius, 1976).

During treatment with propranolol some patients complain of fatigue, muscle weakness, and worsening claudication (Kellaway, 1976; Zacharias, 1976). These side effects in theory may be related to vasodilatation and bronchodilatation during exercise. If the two types of beta-blockers indeed produce

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different effects in this respect, it might be expected that exercise is tolerated better during metoprolol treatment.

For testing these suppositions we investigated the effects of a beta$_1$-selective and a non-selective beta-blocker on haemodynamic and respiratory indices and on perceived exertion during exercise in hypertensive patients. During this study only non-invasive methods were used, in order to avoid stressful stimuli.

Patients

The study included 8 men with untreated essential hypertension, without demonstrable cardiac or pulmonary disease. The initial diastolic blood pressure, measured in the supine position after 15 minutes' bed rest, ranged from 100 to 120 mmHg (mean: 107 mmHg). The average age was 34 years (range 22 to 47). The mean values for height and weight were 1·76 m (range 1·64 to 1·82) and 76 kg (range 62 to 92), respectively. All patients were within 15 per cent of their ideal body weight.

Methods

DESIGN OF STUDY

Propranolol (80 mg thrice daily) and metoprolol (100 mg thrice daily) were compared with each other and with placebo in a double blind cross-over study. In these doses these drugs are considered to be equipotent in reducing heart rate during rest and exercise (Johnsson *et al.*, 1975a; Bengtsson, 1976). There were 4 consecutive periods of medication, each lasting 4 weeks: placebo, beta-blocker, placebo, beta-blocker. The effective agents were given in randomised order. At the end of each 4-week period the same set of investigations (see below) were performed. After this cross-over study 7 patients continued treatment with a beta-blocker in the same dose: 5 preferred metoprolol and 2 propranolol. After 6 months of treatment these investigations were repeated.

The investigations were carried out in a room with a constant temperature of 19 °C, starting at 9 am, two hours after ingestion of the morning dose. The patients were asked to take a light breakfast without coffee and to abstain from smoking. To begin with, blood pressure and heart rate were measured after 15 minutes' bed rest. Next, the effects of an adrenaline infusion on blood pressure, heart rate, and blood flow in the forearm were measured. The results of this part of the investigation are published separately (van Herwaarden *et al.*, 1977). The exercise test started at 10.30 am, a good half hour after stopping the adrenaline infusion. During moderate exercise haemodynamic and respiratory studies were performed.

EXERCISE TEST

Exercise was performed in the sitting position on a bicycle ergometer (Lode^R), with a pedalling frequency of 60 cycles per minute. Before the start of the cross-over study we checked that the load of 1·5 W/kg bodyweight did represent a 'moderate' state of exercise. For this study 'moderate exercise' was arbitrarily defined as exercise with a heart rate below 150 beats per minute. The load of 1·5 W/kg was too heavy for 1 of our 8 patients and for him a load of 1 W/kg bodyweight was chosen. This load was built up within 2 minutes by increments of 0·5 W/kg and then it was maintained during 13 minutes. Measurements were performed during steady state exercise.

RESPIRATORY AND HAEMODYNAMIC INDICES

The expiratory peak flow rate (maximal value of 3 observations) was measured before and after 6 minutes of exercise with the aid of a Wright peak flow meter. After 7 minutes of exercise expired gas was collected in a Douglas bag for 2 minutes. After analysis of CO_2 (Uras) and O_2 (Servomex OA 272) CO_2 production ($\dot{V}CO_2$) and O_2 consumption ($\dot{V}O_2$) were calculated and converted to STPD. Further respiratory rate (f) was measured and tidal volume (V_t) was calculated at BTPS. The arterial CO_2 pressure (P_aCO_2) was determined indirectly using the formula of Bohr for physiological dead space, in which values for the dead space were substituted according to the data of Asmussen and Nielsen (1956). The mixed venous CO_2 pressure ($P_{\bar{v}}CO_2$) was determined indirectly via the rebreathing procedure according to the plateau method of Collier (1956). During this rebreathing procedure CO_2 tension of respired gas was continuously recorded by means of a rapid infrared CO_2 analyser (Capnograph Godart type MO). The $P_{\bar{v}}CO_2$ was calculated from the plateau CO_2 tension after correction for the alveolar-arterial CO_2 pressure difference according to Jones *et al.* (1972). The venoarterial CO_2 content difference ($C_{\bar{v}}CO_2 - C_aCO_2$) was calculated by substituting $P_{\bar{v}}CO_2$ and P_aCO_2 in the computer programme for CO_2 dissociation according to Godfrey (1970). In this computer programme the following values for arterial blood of healthy subjects during moderate exercise were assumed: haemoglobin 15 g/dl; O_2 saturation 0·95; pH 7·4, and base-excess −2·5 mmol/l (Barr *et al.*, 1964; Doll *et al.*, 1966).

The cardiac output was determined by employing Fick's principle for CO_2 and dividing $\dot{V}CO_2$ by $C_{\bar{v}}CO_2 - C_aCO_2$. The venoarterial O_2 content difference was calculated by dividing the O_2 consumption by the cardiac output. An electrocardiogram was recorded every minute. The blood pressure was measured noninvasively with the Physiometrics SRII. This device detects Korotkoff sounds by a microphone, which is placed under a rigid cuff. The low frequency vibrations (16 to 33 Hz) of the sounds are used as signals and recorded on a circular graduated disc. Similar techniques have been proved to produce reliable blood pressure recordings during submaximal exercise (Mastropaolo *et al.*, 1964; Sime *et al.*, 1975; own observations). The recorded blood pressure was the mean of two measurements after 7 and 9 minutes of exercise. The mean arterial pressure was calculated by addition of one-third of the pulse pressure to the diastolic pressure. The total peripheral resistance was calculated by dividing the mean arterial pressure by the cardiac output and was expressed in arbitrary units.

PERCEIVED EXERTION

For rating of perceived exertion the scale described by Borg (1970) was used. This R.P.E. scale consists of 15 grades from 6 to 20. Every second number is accompanied by descriptive words as follows: 7: very very light, 9: very light, 11: fairly light, 13: moderately hard, 15: hard, 17: very hard, and 19: very very hard. The scores and descriptions were printed on a chart. After 4 and 14 minutes of exercise the patients were asked to indicate their score of the perceived exertion.

STATISTICS

All results are presented as mean ± SEM. As the values appeared to be divided normally, statistical analysis was carried out with Student's t test for paired observations. The effects of the two beta-blockers were compared with each other and with the placebo period preceding the period with that particular beta-blocker.

Results

CROSS-OVER STUDY PROPRANOLOL VERSUS METOPROLOL

The data of the four periods are presented in Tables 1, 2, and 3. No significant differences were found between the values recorded in the two placebo periods. Propranolol and metoprolol equally reduced the blood pressure, heart rate, and cardiac output during exercise (Table 1). The stroke volume increased during beta-blockade, while peripheral resistance did not change. These haemodynamic changes in relation to the placebo values are graphically presented in the Fig. Systolic pressure appears to decrease more during propranolol medication than during metoprolol treatment. The mixed venous CO_2 pressure ($P_{\bar{v}}CO_2$) increased during both types of beta-blockade, as did the venoarterial O_2 and CO_2 gradients. The arterial CO_2 pressure (P_aCO_2) was slightly higher during treatment with metoprolol than during the placebo period. Neither beta-blocking agent caused significant differences in the O_2 consumption ($\dot{V}O_2$), CO_2 production ($\dot{V}CO_2$), tidal volume (V_t), and respiratory rate (f) (Table 1).

The expiratory peak flow rate was in every period higher during exercise than at rest (Table 2). Propranolol decreased expiratory peak flow rate at rest as well as during exercise. Metoprolol did not influence the peak flow rate. However, no statistically significant differences were found between the

Table 1 *Respiratory and haemodynamic parameters during exercise after 4 weeks placebo followed by 4 weeks beta-blockade (mean ± SEM, n = 8)*

	Placebo	*Propranolol*	*P**	*Placebo*	*Metoprolol*	*P†*	*P‡*
Cardiac output (l/min)	13·4 ± 0·7	11·4 ± 0·6	< 0·005	13·8 ± 0·7	11·7 ± 0·6	< 0·001	NS
Heart rate (beats/min)	130 ± 5	95 ± 3	< 0·001	127 ± 4	94 ± 2	< 0·001	NS
Stroke volume (ml)	105 ± 7	121 ± 7	< 0·001	110 ± 6	125 ± 8	< 0·05	NS
Systolic pressure (mmHg)	204 ± 4	161 ± 5	< 0·001	197 ± 5	168 ± 5	< 0·001	0·05 < P < 0·1
Mean arterial pressure (mmHg)	132 ± 1	113 ± 2	< 0·001	130 ± 3	113 ± 2	< 0·001	NS
Diastolic pressure (mmHg)	97 ± 2	89 ± 2	< 0·02	96 ± 3	86 ± 2	< 0·01	NS
Total peripheral resistance (units)	10·1 ± 0·6	10·1 ± 0·5	NS	9·5 ± 0·4	9·8 ± 0·4	NS	NS
$P_{\bar{v}}CO_2$ (mmHg)	66 ± 1	72 ± 1	< 0·001	65 ± 1	72 ± 1	< 0·001	NS
P_aCO_2 (mmHg)	37 ± 2	38 ± 1	NS	36 ± 2	39 ± 1	< 0·05	NS
$C_{\bar{v}}CO_2 - C_aCO_2$ (ml/100 ml)	11·8 ± 0·5	13·6 ± 0·5	< 0·001	11·8 ± 0·5	13·4 ± 0 3	< 0·001	NS
$C_aO_2 - C_vO_2$ (ml/100 ml)	12·1 ± 0·4	14·3 ± 0·8	< 0·005	12·0 ± 0·3	13·9 ± 0·4	< 0·005	NS
$\dot{V}O_2$ (l/min)	1·62 ± 0·10	1·63 ± 0·13	NS	1·65 ± 0·08	1·63 ± 0·10	NS	NS
$\dot{V}CO_2$ (l/min)	1·58 ± 0·11	1·54 ± 0·10	NS	1·64 ± 0·10	1·57 ± 0·10	NS	NS
V_t (l)	2·2 ± 0·2	2·4 ± 0·2	NS	2·6 ± 0·3	2·4 ± 0·2	NS	NS
f (breaths/min)	21 ± 3	19 ± 2	NS	20 ± 3	19 ± 2	NS	NS

P* Propranolol versus placebo.
P† Metoprolol versus placebo.
P‡ Metoprolol versus propranolol.
NS P > 0·10.

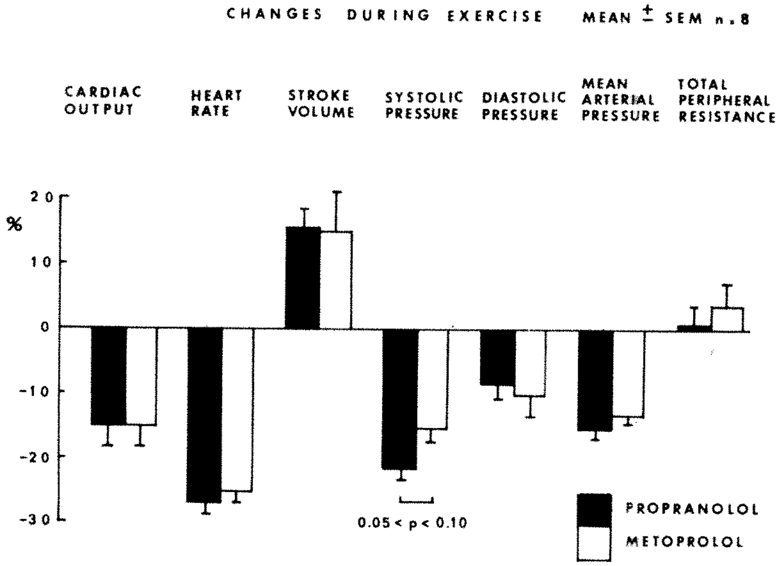

Fig. *Changes of haemodynamic indices during exercise after 4 weeks of beta-blockade compared with placebo values.*

values of the propranolol and metoprolol periods. Neither beta-blocking agent significantly affected the exercise induced increase of the peak flow rate (ΔPFR).

Ratings of perceived exertion after 4 and 14 minutes of exercise and the simultaneously recorded heart rates are presented in Table 3. Heart rate was clearly decreased during beta-blockade ($P < 0{\cdot}001$). Neither propranolol nor metoprolol influenced significantly the RPE scores (sign-test).

OBSERVATIONS AFTER 6 MONTHS OF BETA-BLOCKADE

The haemodynamic indices after 6 months of metoprolol medication were comparable with those measured after 4 weeks of metoprolol treatment (Table 4). The cardiac output after 6 months was possibly slightly higher than after 4 weeks of treatment.

The $P_{\bar{v}}CO_2$ after 6 months was lower and this tendency was also found in the venoarterial CO_2 and

Table 2 *Expiratory peak flow rate (PFR) at rest and during exercise after 4 weeks placebo followed by 4 weeks beta-blockade (mean ± SEM, n = 8)*

	Placebo	*Propranolol*	*P**	*Placebo*	*Metoprolol*	*P†*	*P‡*
PFR at rest (l/min)	563 ± 21	540 ± 20	< 0·05	558 ± 16	557 ± 16	NS§	NS
PFR during exercise (l/min)	592 ± 18	568 ± 20	< 0·05	581 ± 18	574 ± 15	NS	NS
Δ PFR (l/min)	29 ± 7	28 ± 10	NS	23 ± 4	18 ± 6	NS	NS
P exercise versus rest	< 0·01	< 0·05		< 0·001	< 0·05		

P* Placebo versus propranolol.
P† Placebo versus metoprolol.
P‡ Metoprolol versus propranolol.
§ P > 0·10.

Table 3 *Ratings of perceived exertion (RPE) and heart rate at 4 and 14 minutes of exercise after 4 weeks placebo followed by 4 weeks beta-blockade (mean ± SEM, n = 8)*

	Placebo	*Propranolol*	*Placebo*	*Metoprolol*
4 Minutes				
RPE	12·0 ± 0·5	12·0 ± 0·6	11·5 ± 0·8	12·0 ± 0·6
Heart rate	121 ± 4	90 ± 2	118 ± 3	89 ± 2
14 Minutes				
RPE	13·4 ± 0·4	13·8 ± 0·4	12·5 ± 0·4	13·1 ± 0·3
Heart rate	134 ± 4	97 ± 3	131 ± 4	95 ± 2

Table 4 *Respiratory and haemodynamic indices during exercise after 4 weeks and 6 months of treatment with metoprolol compared with placebo values (mean ± SEM, n = 5)*

	Placebo	*4 Weeks*	*P**	*6 Months*	*P†*	*P‡*
Cardiac output (l/min)	13·4 ± 1·0	11·2 ± 0·9	< 0·02	12·2 ± 0·8	< 0·05	0·05 < P < 0·1
Heart rate (beats/min)	128 ± 7	93 ± 3	< 0·01	95 ± 2	< 0·01	NS
Stroke volume (ml)	106 ± 10	122 ± 12	NS	127 ± 9	< 0·02	NS
Mean arterial pressure (mmHg)	130 ± 4	112 ± 3	< 0·01	116 ± 1	< 0·01	NS
Total peripheral resistance (units)	9·9 ± 0·5	10·1 ± 0·6	NS	9·7 ± 0·6	NS	NS
$P_{\bar{v}}CO_2$ (mmHg)	64 ± 2	71 ± 2	< 0·01	67 ± 1	0·05 < P < 0·1	< 0·05
P_aCO_2 (mmHg)	35 ± 2	38 ± 2	< 0·05	36 ± 2	NS	NS
$C_{\bar{v}}CO_2 - C_aCO_2$ (ml/100 ml)	11·9 ± 0·7	13·2 ± 0·8	< 0·05	12·6 ± 0·5	< 0·05	0·05 < P < 0·1
$C_aO_2 - C_{\bar{v}}O_2$ (ml/100 ml)	11·7 ± 0·5	13·4 ± 0·3	< 0·05	12·6 ± 0·05	NS	0·05 < P < 0·1

P* Metoprolol versus placebo.
P† Metoprolol versus placebo.
P‡ Metoprolol 4 weeks versus metoprolol 6 months.
NS P > 0·10.

O_2 differences. The other respiratory indices and the RPE scores were not changed after 6 months of treatment with metoprolol. The measurements in the two patients after 6 months of propranolol treatment showed results comparable with those after 4 weeks of treatment. These values from only two patients are not compiled statistically.

Discussion

The doses of the two beta-blockers used in this study induced the same reduction in heart rate during exercise. This finding is in agreement with previous results (Johnsson *et al.*, 1975a; Davidson *et al.*, 1976). The drugs were given during a four-week period, which is sufficiently long for evaluation of the anti-hypertensive effect of beta-blockers (Zacharias and Cowen, 1970; Hansson *et al.*, 1974). Our results are in agreement with another study which showed that propranolol and metoprolol equally reduce the blood pressure during exercise (Davidson *et al.*, 1976).

Increased sympathetic activity plays an important role in the adaptation of the circulation during exercise (Bevegård and Shephard, 1967). Beta-blockers decrease the heart rate and cardiac output during exercise. The beta$_1$-selective metoprolol induced the same changes in heart rate, cardiac output, and stroke volume as the non-selective beta-blocker propranolol. This could be expected, because metoprolol and propranolol both block the cardiac adrenoreceptors. However, the remarkable finding was that both beta-blockers equally reduced the blood pressure. Apparently, there was no difference in the effect of the two drugs on the peripheral resistance which, during exercise, showed no change from the normal.

During exercise total peripheral resistance decreases by vasodilatation in active muscles, and this is induced by a local mechanism (Bevegård and Shephard, 1967). In other parts of the body such as the 'non-active' muscles a reflex vasoconstriction appears (Bevegård and Shephard, 1967). It was not clear how far vascular beta$_2$-receptors figured in the vascular adaptation during exercise.

It has been established that propranolol blocks the vascular beta$_2$-receptors for circulating catecholamines, whereas metoprolol has a much less pronounced effect (Johnsson, 1975; van Herwaarden *et al.*, 1977). The fact that neither the beta$_1$-selective metoprolol nor the non-selective propranolol influenced the total peripheral resistance shows that stimulation of the vascular beta$_2$-receptors does not play an important part in the adaptation of the circulation during steady-state exercise.

During exercise bronchodilatation occurs; this may be induced by the increased sympathetic tone (Lefcoe, 1969). A consequence of this is the increase in the expiratory peak flow rate (ΔPFR) during exercise as recorded in this study. Propranolol decreased the peak flow rate at rest and during exercise, while metoprolol had hardly any influence. Analogous results were published after administration of propranolol and the beta$_1$-selective practolol (Kumana *et al.*, 1974). These observations are probably related to the fact that metoprolol has a much less pronounced affinity for the bronchiolar beta$_2$-receptors than propranolol (Johnsson *et al.*, 1975b; Tivenius, 1976). However, the propranolol induced reduction of peak flow rate does not seem of functional significance because ventilation was not influenced; after all, asthmatic patients ventilate during exercise with a smaller tidal volume and faster respiratory rate (Haynes *et al.*, 1976). The increase of the expiratory peak flow rate during exercise was not influenced by propranolol or by metoprolol. Therefore, it seems probable that this bronchodilatation during moderate exercise is not mediated via stimulation of the bronchiolar beta$_2$-receptors, but via some other mechanism.

The O_2 consumption and the CO_2 production were not influenced by beta-blocking agents. There was an increase in venoarterial O_2 and CO_2 difference, associated with decreased cardiac output and decreased blood flow through the body. The blood is used more intensively as a transport medium during beta-blockade. It is not surprising that propranolol may cause a worsening of claudication (Zacharias, 1976) in patients with peripheral atherosclerosis as a result of sluggish blood flow. Since metoprolol and propranolol both equally influence the circulation during exercise, this adverse effect could be expected also during metoprolol treatment.

Other side effects such as fatigue and muscle weakness (Kellaway, 1976; Zacharias, 1976) may be associated with this decreased blood flow in muscle tissue.

The heart rate during exercise is often used as a measure for the relative load (Holmgren, 1956). Borg (1970) has so chosen the scores of his RPE scale that these multiplied by 10 represent the heart rate. This relation was seen also in our patients during the placebo periods, but was lacking during beta-blockade (Table 3). Both beta-blockers did not influence the RPE scores. This suggests that this moderate exercise was not perceived as being heavier during beta-blockade. On the other hand, this observation supports the idea that other factors besides heart rate influence perceived exertion (Ekblom and Goldbarg, 1971; Noble *et al.*, 1973). In any case the relation between heart rate and perceived exertion appears to be disturbed by beta-blockade (Ekblom and Goldbarg, 1971).

The results after a half year of treatment with metoprolol were not essentially different from those after 4 weeks of medication. Only the cardiac output showed a tendency to return to the initial value of the placebo period. This effect of long-term beta-blocker medication is well known (Tarazi and Dustan, 1972; Atterhög *et al.*, 1977). However, there was no decrease in the total peripheral resistance even after 6 months. Thus it may be that the antihypertensive effect is still caused by a decrease in cardiac output.

As far as their practical use is concerned, this study suggests no advantage for one or the other of these beta-blocking drugs. The investigations of the haemodynamic effects of adrenaline however argue in favour of the use of beta$_1$-selective blockers rather than non-selective beta-blockers in the treatment of hypertensive patients (van Herwaarden *et al.*, 1977). From a physiological point of view this study does not suggest an important role for the vascular and bronchiolar beta$_2$-adrenoreceptors in the adaptation of circulation and ventilation to steady state exercise.

Metoprolol was kindly provided by Astra Pharmaceutica Holland as Selokeen (= Betaloc = Beloc) tablets.

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Baroreflex sensitivity in hypertension during beta-adrenergic blockade

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SUMMARY Baroreceptor function was measured in 18 patients with essential hypertension by plotting the change in pulse interval against a phenylephrine-induced transient rise in systolic blood pressure. The influence of propranolol (160 mg daily for at least 4 weeks) on this function and on heart rate after maximal exercise was studied and correlated with the plasma propranolol level. In 13 out of the 18 patients only baroreflex resetting occurred with no change in sensitivity during propranolol administration. A definite correlation was found between the degree of beta-adrenergic blockade, expressed as the reduction in maximal exercise heart rate and the change in mean arterial pressure. No relation could be shown between plasma propranolol steady state levels and these changes. The fall in blood pressure during beta-adrenergic blockade with a low dosage of propranolol apparently does not depend on changed baroreflex sensitivity, but on the intrinsic action of this drug on beta-receptors.

Beta-adrenergic blocking agents lower blood pressure effectively, but their mode of action remains obscure. The antihypertensive effect has variously been ascribed to a reduction in cardiac output (Frohlich *et al.*, 1968) or renin activity (Bühler *et al.*, 1972), but the relative importance of these changes has been disputed. Theories based on a central mechanism of action remain controversial (Offerhaus and van Zwieten, 1974; Meyers *et al.*, 1975), while Prichard proposed that a gradual conditioning of the baroreceptors by the damping of pressor responses to regulate the blood pressure at a lower level might be the most likely explanation (Prichard and Gillam, 1966).

We therefore studied the baroreflex sensitivity in hypertensive patients before and during treatment with a beta-adrenergic blocking drug (propranolol). Such sensitivity can be measured repeatedly by plotting the rise in blood pressure after a bolus injection of phenylephrine against the concomitant decrease in heart rate (Bristow *et al.*, 1969; Smyth *et al.*, 1969). Reflex changes were correlated with the degree of beta-adrenergic blockade, determined by the heart rate reduction during exercise and the plasma levels of propranolol.

Patients and methods

Baroreflex sensitivity was measured before and after 4 to 6 weeks of treatment with propranolol 80 mg orally twice daily in 18 outpatients who gave informed consent. All had essential hypertension (diastolic pressure between 100 and 130 mmHg). Their ages were 25 to 69 years, mean 43. All other medication was stopped two weeks before the first measurement and patients were advised to moderate their dietary sodium intake.

Intra-arterial blood pressure and electrocardiograms were recorded simultaneously on a multichannel ink-jet writer at a paper speed of 50 mm/s.

Between 3 and 5 bolus injections of phenylephrine, 200 μg, were given through an intravenous cannula in an antecubital vein. The interval between the injections always exceeded 5 minutes. During the rapid rise in blood pressure after injection, baroreflex sensitivity was calculated by plotting the RR interval against the systolic pressure of the preceding beat. Measurements were made from the moment arterial pressure began to rise acutely until it reached its peak, and the linear correlation between these points was then calculated using the method of least squares. Reflex sensitivity was expressed as the slope of the regression line, and the result was included only if the P value was less than 0·05 and the correlation coefficient was greater than 0·60. Occasionally these conditions were not met.

Baroreceptor function can be modified in two ways. When the slope of the relation between arterial pressure and pulse interval remains unaltered, the regression lines before and during

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treatment are parallel, indicating that baroreflex sensitivity is unchanged. The shift observed is called resetting. On the other hand, a change in the slope of the regression line during treatment is indicative of an alteration in the sensitivity of the reflex arc. A combination of resetting and a change in sensitivity is also possible. For practical reasons in our experiments resetting was calculated as the percentage change in the systolic arterial pressure at an RR interval of 1000 ms.

All patients performed a multistage maximal exercise treadmill test according to the Bruce protocol (Bruce *et al.*, 1963) before and during treatment. The degree of beta-adrenergic blockade was calculated as the percentage reduction in heart rate at maximal exercise during treatment with propranolol.

After 4 to 6 weeks of treatment plasma propranolol levels were measured in 16 patients in the fasting state and 2, 3, 4, 5, and 6 hours after administration of propranolol 80 mg orally. The mean steady state concentration was calculated from the area under the curve, divided by the dosage interval; the plasma propranolol concentration was determined by a modified fluorimetric method (Offerhaus and van der Vecht, 1976).

Statistical analysis was performed using the t test for unpaired data, with Bessel correction for small numbers.

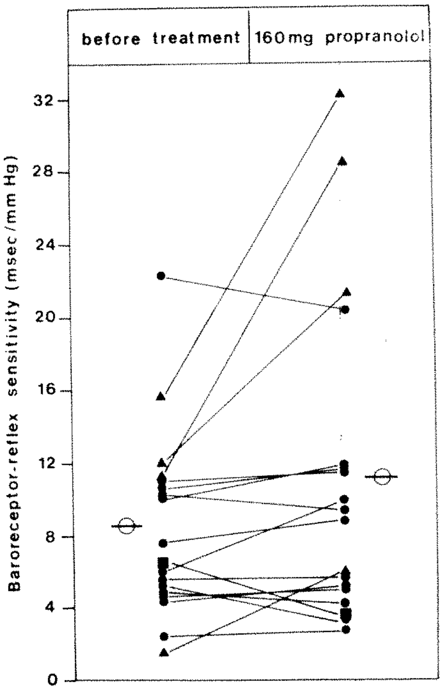

Fig. 1 *Baroreceptor-reflex sensitivity before and during propranolol therapy. Four patients show increased sensitivity* (▲), *13 no significant change* (●), *and 1 a decrease in sensitivity* (■). *The open circles represent the mean values for all patients.*

Results

As expected, both mean arterial pressure and heart rate at rest and during exercise decreased after 4 to 6 weeks of propranolol, 160 mg daily (Table 1). Baroreflex sensitivity did not change significantly in the group as a whole, though in 4 patients there was a significant increase above control values (group B) (Fig. 1). In 13 patients (group A) there was only resetting of the baroreceptors, since propranolol lowered heart rate and blood pressure equally. One patient showed a decrease in baroreceptor sensitivity. The 4 patients with increased sensitivity also showed baroreceptor resetting (Fig. 2). When resetting was plotted against the reduction in maximal heart rate or mean arterial pressure, two linear relations were obtained (Fig. 3), showing the relative contributions of changes in heart rate and blood pressure to such resetting. There was no significant difference between groups A and B with regard to age, initial mean arterial pressure, pretreatment baroreflex sensitivity, heart rate, and blood pressure reduction during propranolol treatment, or in the mean steady state concentration of plasma propranolol (64 ± 8 versus 84 ± 19 ng/ml, NS). However, in group A the transient rise in blood pressure after phenylephrine was augmented during propranolol treatment, but this phenomenon was not seen in the 4 patients with both resetting and increased sensitivity (Table 2).

Table 1 *Effects of propranolol on haemodynamics (mean ± SEM) in 18 patients*

	Before treatment	*Propranolol 160 mg/day*	*Significance of change*
Mean arterial pressure (mmHg)	123 ± 4	111 ± 3	$P < 0{\cdot}05$
Resting heart rate (b/min)	72 ± 2	57 ± 2	$P < 0{\cdot}001$
Maximal heart rate during exercise (b/min)	162 ± 4	126 ± 4	$P < 0{\cdot}001$
Baroreceptor reflex sensitivity (ms/mmHg)	8·53 ± 1·18	11·17 ± 2·06	NS
Systolic arterial pressure at RR interval of 1000 ms (mmHg)	206 ± 10	149 ± 7	$P < 0{\cdot}001$
Phenylephrine induced rise in systolic arterial pressure (mmHg)	40 ± 3	51 ± 3	$P < 0{\cdot}05$

In all patients an inverse correlation was found,

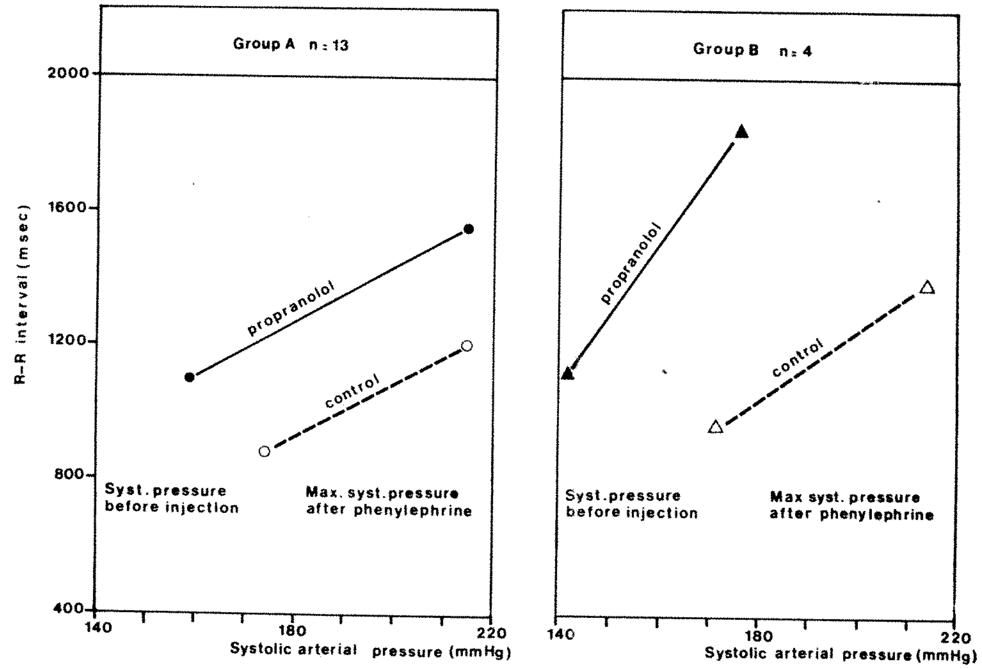

Fig. 2 *Influence of propranolol on baroreceptor reflex function. The slope of the lines represents the means of baroreceptor reflex sensitivities before (open symbols) and during (closed symbols) propranolol treatment. In group A (○) the slopes are not significantly different and the lines are parallel (resetting). In group B (△) there is a significant ($P < 0{\cdot}05$) difference between the slopes (resetting and change in sensitivity).*

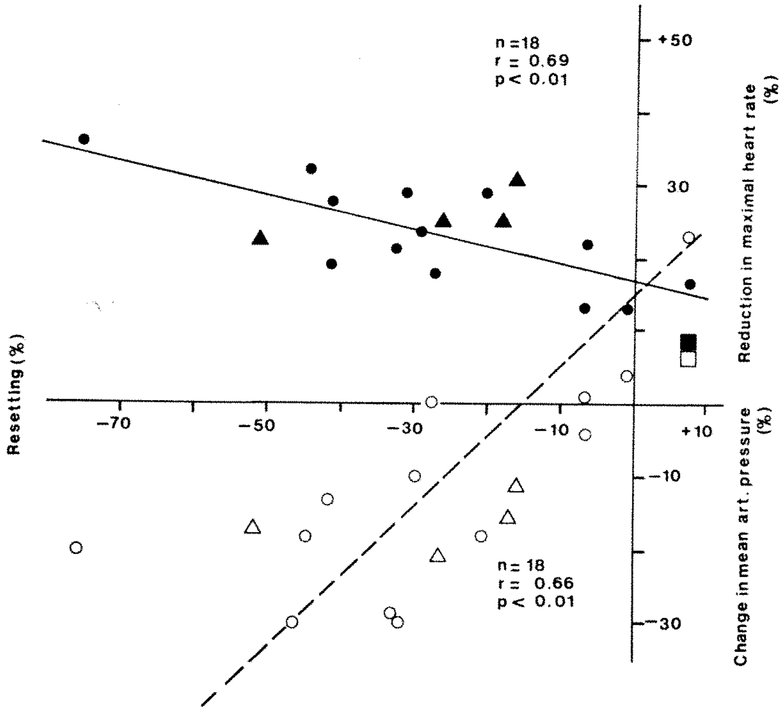

Fig. 3 *Relation between resetting versus beta-blocking and antihypersensitive properties of propranolol. In all 18 patients a correlation was found between the degree of resetting versus the percentage reduction in maximal heart rate during exercise (closed symbols) and the change in mean arterial pressure (open symbols). The form of the symbols refers to Fig. 1.*

Table 2 *Response to alpha-adrenergic stimulation in group A and B before and during propranolol treatment (mean ± SEM)*

	Group A *n = 13*	*Group B* *n = 4*	
Phenylephrine induced rise in systolic arterial pressure before treament (mmHg)	39 ± 2	42 ± 13	NS
Phenylephrine induced rise in systolic arterial pressure during propranolol 160 mg daily (mmHg)	55 ± 3	33 ± 6	P < 0·01
	P < 0·001	NS	

both before and during propranolol treatment, between baroreflex sensitivity and the rise in systolic arterial pressure after phenylephrine (P < 0·01).

Plotting the change in mean arterial pressure during propranolol treatment against the heart rate reduction during maximal exercise yielded a definite linear relation (Fig. 4). No correlation was found between the propranolol mean steady state concentration and the antihypertensive effect or the reduction in heart rate at rest, or during maximal exercise.

Discussion

The influence of propranolol on baroreceptor function has previously been studied by Pickering *et al.* (1972), who found an increase in baroreflex sensitivity after intravenous propranolol in 4 of 5 healthy volunteers. We found no change in the majority of our hypertensive patients during chronic oral treatment with propranolol, using their method of determining baroreflex sensitivity. This finding confirms the results of Simon *et al.* (1977) who were also unable to find increased sensitivity in their hypertensive patients after propranolol intravenously. The difference between our results and those of Pickering *et al.* (1972) may be attributable to the low pretreament sensitivity values in our group showing only resetting (group A)—about one-third of those in the healthy volunteers given propranolol intravenously—and to the fact that such values decrease with age and the severity of hypertension. In 3 of our 4 patients who responded with increased sensitivity, the initial value lay far above the mean (Fig. 1).

The propranolol-induced excessive rise in blood pressure after phenylephrine in those patients showing no change in sensitivity may possibly have been the result of unopposed peripheral alpha-adrenergic activity. The fact that this rise was absent

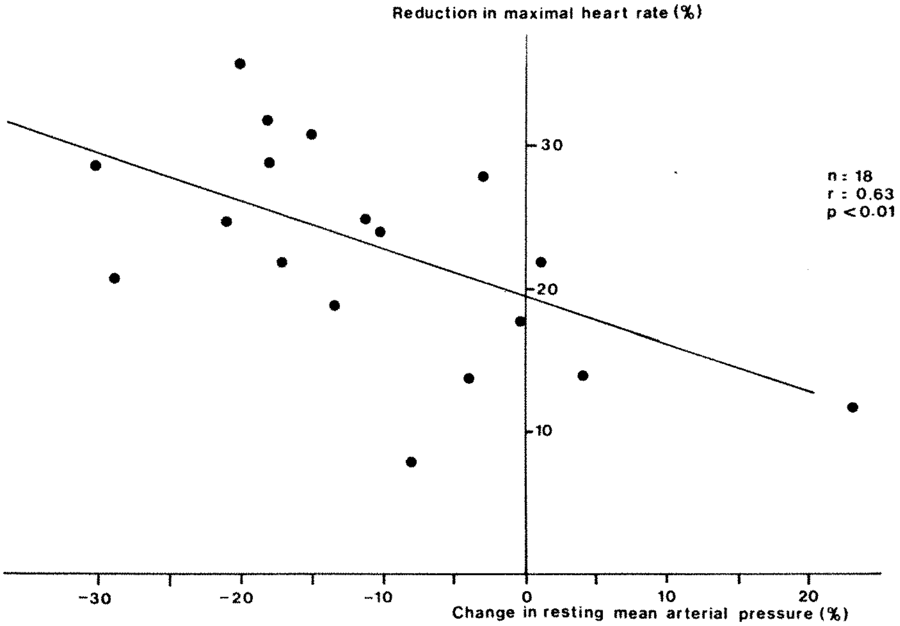

Fig. 4 *Correlation between the decrease in blood pressure and the reduction in maximal exercise heart rate during treatment with propranolol.*

in the 4 patients with increased sensitivity on propranolol indicates that a sensitive baroreflex system, functioning normally, protects against an excessive blood pressure response provoked by alpha-adrenergic stimulation, for example by phenylephrine or the cold pressor test (Guazzi *et al.*, 1976).

Although some investigators (Coltart and Shand, 1970; Pine *et al.*, 1975) have reported a linear relation between the degree of beta-adrenergic blockade and the logarithm of the plasma propranolol level, no such relation was found in our study between mean steady state propranolol and its effect on maximal exercise heart rate. This discrepancy might be explained by their method of quantifying beta-blockade in a limited number of healthy volunteers on various dosage schedules or, alternatively, by variations in the metabolic clearance or plasma protein binding of the drug.

Functional beta-adrenergic blockade with a standard propranolol regimen was found to be closely related to its antihypertensive effect and a similar observation was made in a study of hypertensive patients treated with five different beta-blocking agents (Davidson *et al.*, 1976). In doses that produced similar reductions in exercise tachycardia, all drugs had identical blood pressure lowering activity which was more pronounced on systolic than diastolic pressure and was greatest during exercise.

We, therefore, conclude that the antihypertensive effect of beta-adrenergic blockade is not explained by changes in baroreflex sensitivity; resetting is the major change in function during administration of low dosages of propranolol. The intrinsic action of this drug on the beta-receptors explains adequately the observed fall in blood pressure.

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Potential value of thallium-201 scintigraphy as a means of selecting patients for the coronary care unit

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SUMMARY The potential value of thallium-201 scintigraphy as a means of selecting patients for appropriate coronary care unit admission was evaluated. Studies were made prospectively on 203 patients with possible acute myocardial infarction but atypical history and non-diagnostic electrocardiogram at a time when the clinical diagnosis was still in doubt. Under conventional circumstances, this particular group of patients will be admitted to the coronary care unit for observation in order to rule out myocardial infarction by further clinical evaluation. Scintigraphy was performed upon arrival in the coronary care unit and within 10 hours after the last episode of chest pain. Of 203 patients, 49 had positive, 47 had questionable, and 107 had normal thallium-201 scintiscans. Serial serum enzyme determinations and further clinical follow-up disclosed acute myocardial infarction in 34 patients: all had abnormal scans. Of 47 patients subsequently determined to present with unstable angina, 27 had abnormal scans, of whom 7 subsequently developed acute myocardial infarction. Of 24 patients with previous myocardial infarction, 18 patients had abnormal scans. None of either the 25 patients with stable angina or the 73 patients with atypical complaints showed frank perfusion defects, though questionable abnormal scintiscans were obtained in 5 and 12 patients in these groups, respectively.

It is concluded that thallium-201 scintigraphy, when performed within a time interval of 10 hours after the last episode of chest pain, may be of value as a means of selecting those patients requiring further stay in hospital and observation in the coronary care unit.

We have reported previously that thallium-201 scintigraphy is a highly sensitive technique for the detection of acute myocardial infarction, especially during the very early period after the onset of symptoms (Wackers *et al.*, 1975, 1976). In addition, a considerable number of patients with unstable angina will show abnormal thallium-201 scintiscans during the pain free period after an anginal attack (Wackers *et al.*, 1978). The purpose of the present study was to assess the potential of thallium-201 scintigraphy to serve as a more appropriate means of selecting patients for admission to the coronary care unit. In many patients, the diagnosis of acute myocardial infarction is obvious at the time of hospital arrival. However, among the patients referred to the coronary care unit of our hospital, a significant number have complaints which are determined subsequently not to be caused by acute coronary artery disease. In many of these patients the history and initial electrocardiogram will provide sufficient information to recognise the non-cardiac character of the complaints. Nevertheless, a substantial group of patients still remains in whom initial evaluation provides a questionable history and a non-diagnostic electrocardiogram; in these patients admission and further clinical observation for at least 24 hours seems unavoidable in order to rule out acute myocardial infarction or ischaemia. In order to maximise efficient management and use of the coronary care unit, early and proper characterisation of patients in whom the diagnosis remains in question is essential. The results of the present study indicate that thallium-201 scintigraphy might be of value as a means of selecting those from within the above-mentioned group of patients who, in fact, require coronary care unit admission and further observation.

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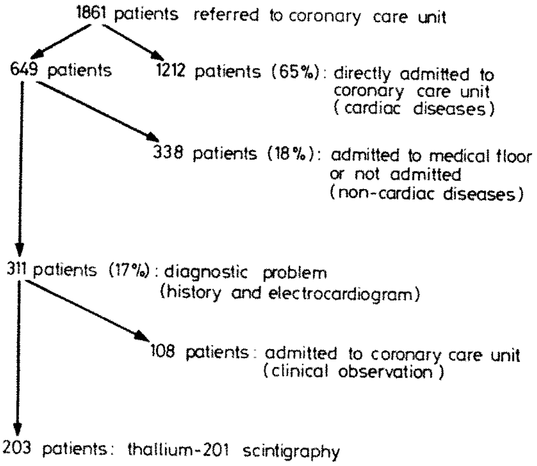
1861 patients referred to coronary care unit
649 patients
1212 patients (65%): directly admitted to coronary care unit (cardiac diseases)
338 patients (18%): admitted to medical floor or not admitted (non-cardiac diseases)
311 patients (17%): diagnostic problem (history and electrocardiogram)
108 patients: admitted to coronary care unit (clinical observation)
203 patients: thallium-201 scintigraphy

Fig. 1 *Admission policy in 1861 patients referred to the coronary care unit. In 203 patients thallium-201 scintigraphy was evaluated as a potential selection method.*

Subjects and methods

A prospective study was performed from September 1975 to September 1976. During this period 1861 patients were referred to the coronary care unit because of presumed acute myocardial infarction. The admission policy for these patients is shown in Fig. 1. There were 1212 patients (65%) who were directly admitted because of evident acute cardiac disease from the history and/or electrocardiogram. In 338 patients (18%) cardiac disease could be ruled out by the history, symptoms, physical examination, and electrocardiogram. These patients were either transferred to other departments or they were allowed to return home. A diagnostic problem was posed by 311 (17%) patients because of atypical history and/or non-diagnostic electrocardiogram. Such patients usually are admitted to the coronary care unit for a further evaluation period of at least 24 hours. In 203 of the 311 patients thallium-201 scintigraphy was performed at arrival in the coronary care unit. In these patients the time interval between the last episode of chest pain and scintigraphy did not exceed 10 hours. Entry into the study of these 203 patients in whom the diagnosis intially was unclear was determined only by the availability of the radiopharmaceutical and the gamma camera. The additional 108 diagnostically undefined patients not studied with thallium-201 were admitted for the usual clinical observation period.

SCINTIGRAPHY

All scintigraphic studies were performed with an Ohio Nuclear ON-100 scintillation camera installed in the coronary care unit. Thallium-201 scintigraphy was performed as soon as possible after arrival of the patients. Using a low energy, high resolution, parallel hole collimator and a 20 per cent energy window set symmetrically over 75 keV, scintiscans were obtained 5 to 10 minutes after intravenous injection of 1·6 to 2·7 mCi thallium-201 chloride. Scintiscans accumulating 300 k counts were obtained in 3 views (anterior 0°, left anterior oblique 45°, and left lateral, the latter with the patient positioned on his right side). The analogue unprocessed images were judged without knowledge of clinical data as positive, questionable, or normal. The judgement concerning diminished or absent regional thallium-201 activity was made qualitatively by comparison of thallium-201 accumulation in different areas of the left ventricular myocardium. The scintiscans read as 'positive' or 'defect', showed a consistent area of definite diminished thallium-201 activity, equal to or less than lung activity, on all three views. 'Questionable' scans represented either a consistent area with diminished activity but slightly higher than background activity on all three views or a defect on only one view. 'Normal' scans showed homogeneous uptake of the radiopharmaceutical in the left ventricle on all three views.

All scintiscans were read by at least two observers. The results in this study represent a consensus of the observers.

ADMISSION POLICY AND FOLLOW-UP

The results of scintigraphy were made available to the attending physician in the coronary care unit and at times affected his final judgment. Of the 203 patients studied, 116 patients were admitted to hospital (63 in the coronary care unit and 53 in the medical floor) and 87 patients were allowed to return home.

All patients admitted to the coronary care unit or medical floor had a similar follow-up for 2 to 3 weeks, while all patients who returned home were seen again after 2 or 3 days, or earlier if either enzyme levels were raised or complaints persisted. In addition, all the latter patients were seen for follow-up after 8 to 12 months (mean 9 months).

ELECTROCARDIOGRAM

Twelve lead electrocardiograms were obtained in all patients at arrival at the coronary care unit, before thallium-201 scintigraphy. The patients who were in hospital had electrocardiograms taken at least twice daily. The patients who returned home all had a follow-up electrocardiogram 2 or 3 days after the scintigraphic study and at the follow-up at 8 to 12 months.

ENZYME DETERMINATIONS

For all patients blood samples were taken approximately at the time of scintigraphy for determination of enzyme levels (SGOT, SGPT, LDH, and CKMB) and subsequently each 6 hours for at least 24 hours in those patients who were in hospital. The patients who returned home all had a second blood sample taken at the second or third day at follow-up.

FINAL DIAGNOSIS

A major objective of this study was to assess the accuracy of thallium-201 scans to detect patients with acute myocardial infarction. Though the remaining patients, without acute infarction, all had an atypical history on admission, further observation allowed separation into several subgroups. The final diagnosis was based upon the results of enzyme level determinations, the development of electrocardiographic changes, and the impression obtained after further clinical evaluation. The following diagnostic criteria were employed.

Acute myocardial infarction

(1) Enzyme levels showing typical rise and fall after admission; (2) electrocardiographic development of diagnostic Q waves (more than 0·03 s in duration), loss of R waves, or T wave inversion.

Unstable angina progressing to acute myocardial infarction

(1) Normal enzyme levels at the time of scintigraphy; (2) the occurrence of a new severe attack of chest pain within 24 hours of admission to hospital, followed by the electrocardiographic development of diagnostic Q waves, loss of R waves, or T wave inversion, and typical rise and fall of enzyme levels.

Unstable angina

(1) Normal enzyme levels during the observation period; (2) upon further questioning, a history suggesting angina pectoris increasing in severity and frequency within a period of approximately 10 days before admission; (3) transient electrocardiographic changes were not required. (*Note:* Since all patients included in this study had an atypical history on admission, the term 'unstable angina' is defined more liberally than usual.)

Previous myocardial infarction

(1) Diagnostic Q waves on the electrocardiogram; (2) normal enzyme levels during the observation period.

Stable angina pectoris

(1) Normal enzyme levels; (2) history of chest pain occurring on exertion and disappearing at rest, relieved by glyceryl trinitrate.

Atypical complaints

(1) Normal enzyme levels; (2) after further questioning it was felt that the complaints had to be interpreted as atypical and most likely of non-cardiac origin.

SENSIVITY, SPECIFICITY, AND PREDICTIVE ACCURACY

The sensitivity of thallium-201 scintiscans was defined as:

$$\frac{\text{True positives (TP)}}{\text{TP + false negatives (FN)}} \times 100$$

The specificity was defined as:

$$\frac{\text{True negatives (TN)}}{\text{TN + false positives (FP)}} \times 100$$

The predictive accuracy of a positive test was defined as:

$$\frac{\text{TP}}{\text{TP + FP}} \times 100$$

Results

SCINTIGRAPHY

The results of thallium-201 scintigraphy were available within 1½ to 2 hours after arrival of the patients in the coronary care unit. Of the 203 patients, 49 had positive, 47 had questionable, and 107 had normal scans.

ELECTROCARDIOGRAM

Except for one patient who had complete left bundle-branch block, all patients showed normal initial ventricular activation pattern on the electrocardiogram at the time of scintigraphy. The electrocardiogram was normal in 78 patients and showed nonspecific ST segment changes in 125 patients. The relation between the scintigraphic results and the electrocardiographic findings is shown in Table 1.

Table 1 *Relation between results of thallium-201 scintigraphy and electrocardiogram in 203 patients*

Scintigraphy	*Electrocardiogram*		*Total*
	Normal	*Nonspecific ST-T segment changes*	
Defect	12	37	49
Questionable	17	30	47
Normal	49	58	107

FINAL DIAGNOSIS

On the basis of serum enzyme determinations, 34 patients (17%) had acute myocardial infarction at the time of scintigraphy. Fourteen of these patients evolved electrocardiographic transmural infarctions with peak SGOT rise of more than 4 times upper limit of normal; of these patients 2 had recurrent infarction. Twenty patients had electrocardiographic non-transmural or biochemically small infarctions (SGOT rise less than 4 times upper limit of normal). Forty-seven patients (23%) had 'unstable angina' at the time of thallium-201 scintigraphy; in 7 of these this progressed to acute myocardial infarction within 24 hours after admission, and 4 out of these 7 patients had electrocardiographic transmural infarctions. The remaining 40 patients with 'unstable angina' all had an unremarkable course. Twenty-four patients (12%) had previous myocardial infarction. Twenty-five patients (12%) were considered to have symptoms of stable angina pectoris. In 73 patients (36%) the final impression was of atypical complaints, most likely of non-cardiac origin.

RELATION BETWEEN FINAL DIAGNOSIS AND RESULTS OF THALLIUM-201 SCINTIGRAPHY (FIG. 2)

All patients determined subsequently to have had acute myocardial infarction at the time of scintigraphy had abnormal scans: 30 patients showed definite defects on the scintiscans, and in the remaining 4 patients the scintiscans were judged as questionable. The 2 patients with recurrent infarction both had positive scans. Of the 7 patients with 'unstable angina' who developed acute myocardial infarction, 5 patients had positive scans, and 2 had questionable scans. Of the remaining 40 patients with uncomplicated 'unstable angina', 5 had positive scans, 15 had questionable scans, and 20 had normal scans. Of the 24 patients with previous myocardial infarction, 9 showed a defect, 9 had questionable scans, and 6 had normal scans. None of the patients with stable angina pectoris or atypical complaints had a defect on the thallium-201 scans. Five of 25 patients with stable angina had questionable scans, the remaining 20 had normal scans. Of the 73 patients with atypical complaints, 12 patients had questionable scans and 61 patients had normal scans. Thus, positive scans were obtained only in patients with acute or previous myocardial infarction or 'unstable angina'. Questionable scans were obtained in 30 of 105 patients with myocardial infarction or 'unstable angina' compared with 17 of 98 patients with stable angina or atypical complaints. This difference is, however, not significant. Normal scans were obtained in 26 of 105 patients with myocardial infarction or 'unstable angina', compared with 81 of 98 patients with stable angina or atypical complaints ($P < 0{\cdot}01$).

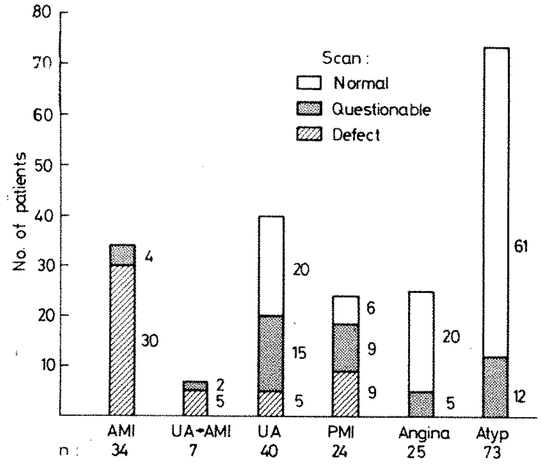

Fig. 2 *Final diagnosis and results of scintigraphy in 203 patients referred to the coronary care unit. The final diagnosis is based on the results of enzyme level determinations, the development of electrocardiographic changes, and the re-evaluation of the patient's history. Abbreviations: AMI, acute myocardial infarction; PMI, previous myocardial infarction; UA, unstable angina, UA → AMI, unstable angina progressing to acute myocardial infarction; atyp, atypical complaints.*

SENSITIVITY, SPECIFICITY, AND PREDICTIVE ACCURACY OF THALLIUM-201 SCINTISCANS

The sensitivity, specificity, and predictive accuracy of thallium-201 scintiscans to detect patients with acute myocardial infarction, 'unstable angina', and previous myocardial infarction are given in Table 2. Positive thallium-201 scans have an 88 per cent

Table 2 *Diagnostic value of thallium-201 scintigraphy for various diagnoses in 203 patients*

Scintiscans	*Diagnosis*	*Sensitivity* (%)	*Specificity* (%)	*Predictive accuracy* (%)
Positive	AMI	88	88	61
	AMI, UA→AMI	85	91	71
	AMI, UA	49	92	81
	AMI,PMI, UA	46	100	100
Positive + Questionable	AMI	100	63	35
	AMI, UA→AMI	100	66	42
	AMI, UA	75	71	63
	AMI, PMI, UA	75	82	82

Abbreviations: AMI, acute myocardial infarction; UA → AMI, unstable angina progressing to AMI; PMI, previous myocardial infarction.

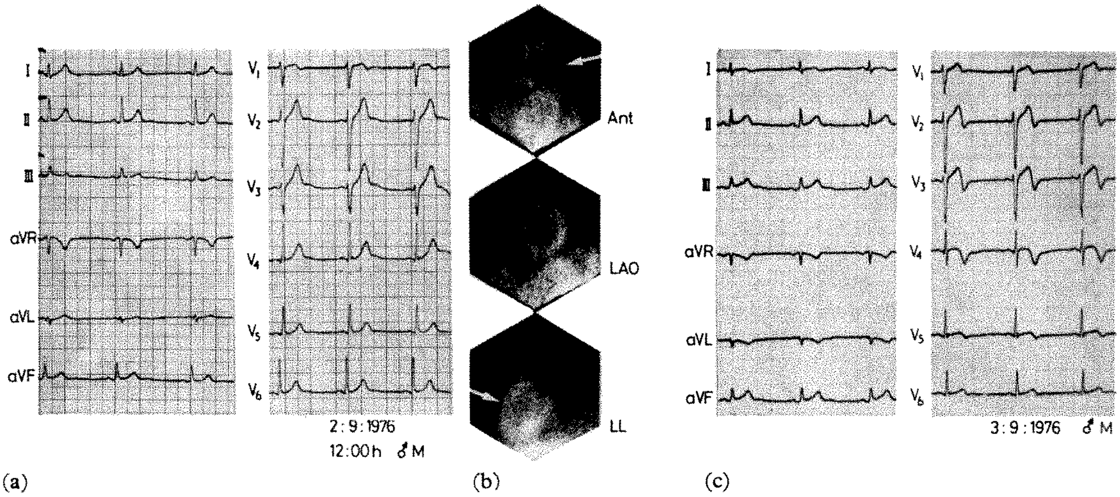

Fig. 3(a) *Electrocardiogram on admission of a 37-year-old man. During the night before admission he experienced recurrent attacks of atypical praecordial pain, which had subsided at admission. Though there is loss of R wave in V3, this electrocardiogram is not diagnostic for acute myocardial infarction.* (b) *Thallium-201 scintiscans at the time of the electrocardiogram in Fig. 3a. An evident area of diminished activity is present at the anterolateral wall (arrows). CKMB level at the same time was raised (10 times the upper limit of normal). Peak SGOT level indicated that the infarction was probably small (2·5 times the upper limit of normal). Abbreviations: Ant, anterior 0° view; LAO, left anterior oblique 45° view; LL, left lateral 90° view.* (c) *Electrocardiogram of the same patient as in Fig. 3a and 3b 24 hours after admission. Changes compatible with acute anterior wall infarction have developed. These changes occurred 10 hours after admission.*

sensitivity, 88 per cent specificity, and 61 per cent predictive accuracy to detect acute myocardial infarction in the particular patient population studied. The sensitivity increases to 100 per cent when questionable scans also are included but then the specificity and predictive accuracy decrease to 63 and 35 per cent, respectively. Positive scans have a specificity of 92 per cent and a predictive accuracy of 81 per cent to detect the group of patients with acute myocardial infarction or 'unstable angina' but the sensitivity is 49 per cent. The sensitivity is 75 per cent in the latter group when questionable scans also are included. The specificity and predictive accuracy to recognise patients in whom perfusion defects may be expected (that is, acute myocardial infarction, 'unstable angina', and previous myocardial infarction) by positive scans are 100 per cent: no false positive scintiscans were obtained. For questionable scans these values were 82 per cent.

Discussion

The present study deals with a common diagnostic dilemma in the coronary care unit or emergency room. Neither the patient's history nor electrocardiogram permitted a definite diagnosis at the time of admission. Yet, 34 patients evolved acute myocardial infarction, and all these patients had abnormal (positive or questionable) thallium-201 scintiscans on admission. Diagnostic electrocardiographic changes occurred in these patients only hours after admission. Fig. 3 shows an example of such a patient. Behar *et al.* (1977) evaluating the electrocardiogram as a decision making tool in a consecutive series of patients in the emergency room reported that 35 per cent of the patients with acute myocardial infarction showed a normal electrocardiogram at arrival in the emergency room.

In the present study, positive thallium-201 scans also were obtained in 10 patients with 'unstable angina' and in 9 patients with previous myocardial infarction. Of the 10 patients with 'unstable angina' and positive scans, 5 developed acute myocardial infarction after being admitted to hospital; similar progression occurred in 2 of 22 patients with 'unstable angina' and questionable scans. The finding of positive scans in patients with unstable angina is in agreement with our results in a larger series of patients with unstable angina, in which positive scans were obtained in 50 per cent of the patients studied within 6 hours after the last anginal attack (Wackers *et al.*, 1978). This is not surprising since thallium-201 uptake in the myocardium reflects regional myocardial perfusion (Strauss *et al.*, 1975;

DiCola *et al.*, 1977) and the integrity of the Na^+K^+-ATPase system (Britten and Blank, 1968; Adolph *et al.*, 1976; Gelbart *et al.*, 1976). This lack of specificity is not necessarily a disadvantage, since both myocardial infarction and unstable angina provide indications for coronary care unit admission.

The design of our study may be criticised since 78 patients were allowed to return home and did not receive the same detailed follow-up in terms of serial enzyme determinations and electrocardiograms as did the 116 patients who were in hospital. The patients who returned home were seen again only after 2 or 3 days. Therefore, we cannot exclude the possibility that transient electrocardiographic changes or slight enzyme rises were undetected in this group. However, in the 116 patients who were in hospital and who were followed up closely, the same excellent agreement existed between final diagnosis and results of thallium-201 scintigraphy as in the patients who returned home. Therefore, it seems unlikely that the results of this study are significantly influenced by this aspect of study design.

The present series of patients represents a highly selected group of patients, in whom neither the electrocardiogram nor the history were diagnostic. Therefore, the value of thallium-201 scintigraphy is maximally challenged. It is in this group of patients that a reliable selection method is needed. A selection procedure for the coronary care unit or emergency room should be able to detect (a) patients with acute myocardial infarction, (b) patients with pre-infarction angina or unstable angina, (c) patients with non-cardiac complaints. The results of this study indicate that thallium-201 scintigraphy might be such a method when positive and questionable scintiscans are considered abnormal. Table 3 illustrates the potential influence of thallium-201 scintigraphy on the admission policy in the coronary care unit. It seems conceivable that in most medical centres the 203 patients would have been admitted to rule out myocardial infarction. If all patients with acute myocardial infarction and unstable angina are to be admitted to the coronary care unit, then in the present study 81 patients should have been admitted to the intensive care unit. The remaining 122 patients (60%) would have been admitted unnecessarily. In contrast, if the results of thallium-201 scintigraphy were used as selection criteria, 96 patients with positive and questionable scans would have been admitted and 107 patients with normal scans would be allowed to return home. Using thallium scintigraphy all patients with acute myocardial infarction and the majority of the patients with 'unstable angina' would have been correctly in hospital, but 35 patients (18 with previous infarction, 5 with stable angina, and 12 with atypical complaints) would have been in hospital unnecessarily. On the other hand, 20 patients with 'unstable angina' would have been allowed to return home. However, it should be emphasised that 'unstable angina' in the present context represents a liberal use of the terminology. Moreover, all patients with 'unstable angina' and normal scans had an unremarkable and favourable clinical course.

Table 3 *Evaluation of admission policy in 203 patients: admission based on electrocardiogram and history is compared with that based on thallium-201 scintigraphy and related to final follow-up diagnosis* (*see text*)

	Destination		*Incorrect*	
	Hospital	*Home*	*Hospital*	*Home*
Electrocardiogram + history	203	—	122 (60%)	—
Thallium-201 scintigraphy	96	107	35 (36%)	20 (18%)
Correct (retrospect)	81 (AMI, UA)	122 (atyp)		

Abbreviations: AMI, acute myocardial infarction; UA, unstable angina; atyp, atypical complaints.

Conclusion

In view of the high cost of the coronary care unit (Peterson, 1976) it could be of value if only those patients with bona fide acute coronary syndromes were admitted. The sensitivity of thallium-201 scintigraphy to detect myocardial perfusion defects indicates that this method might be useful as a selection method for the coronary care unit or emergency room. The standard electrocardiogram may be non-diagnostic during the early hours of an acute infarction in some patients. In addition when abnormal initial ventricular activation pattern is present, such as left bundle-branch block, WPW syndrome, or pacemaker rhythm, the electrocardiographic diagnosis of acute infarction is hampered. Though the use of thallium-201 scintigraphy as a selection method has to be assessed in a prospective controlled study, the following practical guidelines can be given on the basis of the present study: (1) thallium-201 scintigraphy has to be performed within 6 to 10 hours after the last episode of chest pain; (2) in the presence of previous myocardial infarction positive thallium-201 scans have limited value; (3) negative scans within 6 to 10 hours after acute chest pain make acute myocardial infarction unlikely, though acute coronary insufficiency cannot be excluded; (4) positive thallium-201 scans may represent either acute myocardial infarction, previous myocardial infarction, or unstable angina.

Finally, we should like to emphasise that this study deals with a particular subgroup of patients, in whom the history and electrocardiogram were of little help in the decision making. Thallium-201 scintigraphy has to be considered as an additional diagnostic method, along with history and electrocardiogram, to improve efficient management of the coronary care unit.

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Case reports

British Heart Journal, 1979, **41**, 118-120

Echocardiographic findings in prolapsed aortic cusp with vegetation

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From the Departments of Cardiology and Cardiothoracic Surgery, St. Thomas' Hospital, London

SUMMARY A patient with severe aortic regurgitation showed abnormal echoes in the left ventricular outflow tract compatible with aortic vegetation or flail aortic cusp. At operation, a pedunculated vegetation on a prolapsed aortic cusp was found. The case illustrates some of the pitfalls in the echocardiographic distinction of the two conditions.

The distinction on echocardiographic findings between valvular vegetation and aortic valve cusp prolapse is not easy. We report here the echocardiographic features of a patient who had a vegetation on a prolapsed aortic valve cusp.

Case report

The patient, now aged 36, was a West Indian nurse with no history of rheumatic fever. Aortic regurgitation was first detected in 1965 but she was asymptomatic through three subsequent pregnancies. In 1973 she developed subacute bacterial endocarditis. Blood cultures grew *Streptococcus viridans* and she was successfully treated with a six-week course of intravenous penicillin. She made a full recovery but serial electrocardiograms and chest radiographs showed progressive cardiomegaly. Cardiac catheterisation in May 1975 confirmed severe aortic regurgitation.

Aortic valve replacement was performed in July 1975. All three aortic valve cusps were slightly thickened. The right coronary cusp had a 3 mm perforation in the centre. The left coronary cusp was prolapsed with a pedunculated mass of vegetation, 4 mm in diameter, attached to its free edge (Fig. 1). The valve was excised and replaced with a Starr Edwards prosthesis. Bacteriological culture of the valve tissue and vegetation was negative. She made an uneventful recovery and has since returned to work.

ECHOCARDIOGRAPHIC FINDINGS

Echocardiograms were obtained the day before

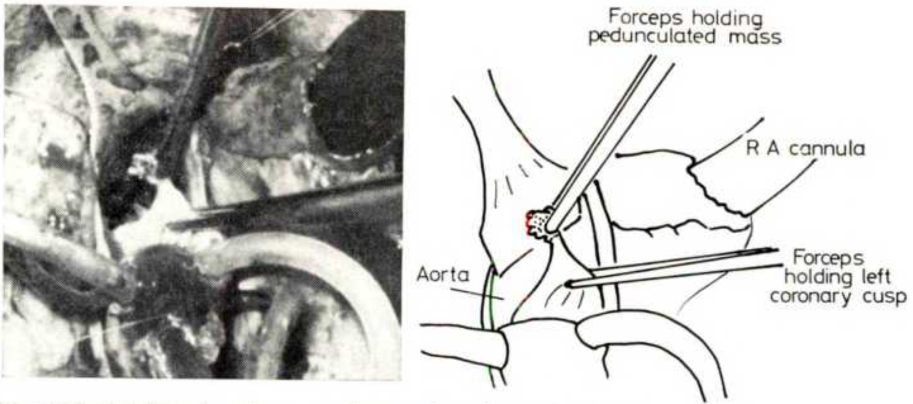
Forceps holding pedunculated mass
R A cannula
Aorta
Forceps holding left coronary cusp

Fig. 1 *Photograph of prolapsed aortic cusp and vegetation taken at the time of operation.*

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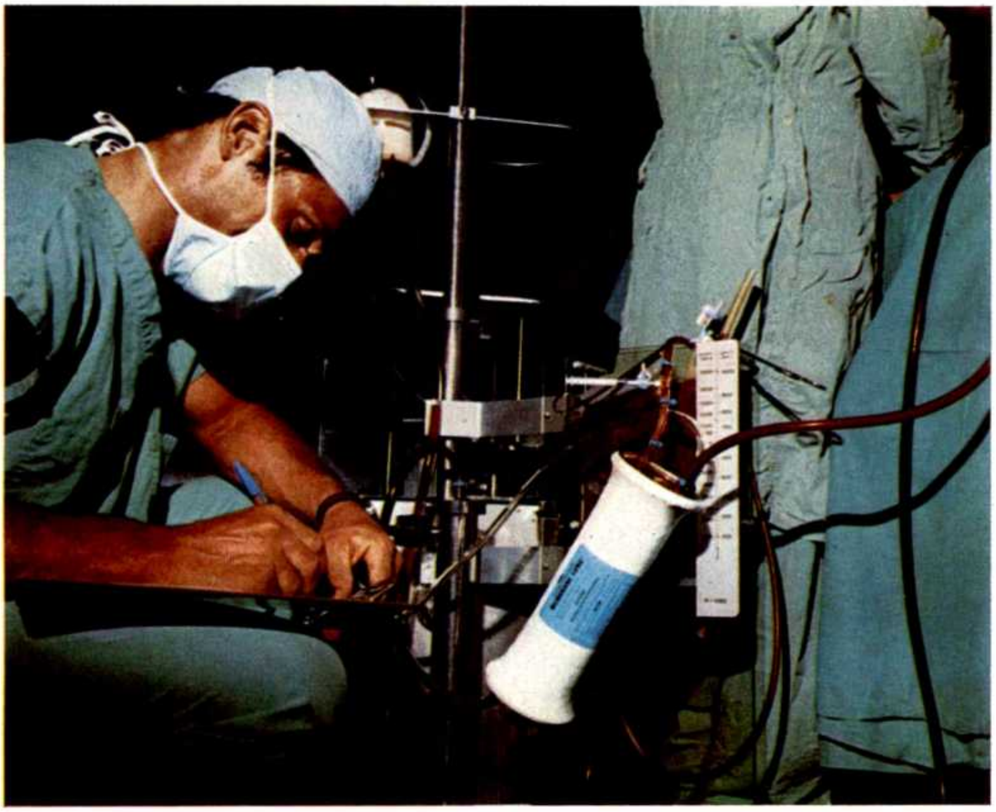

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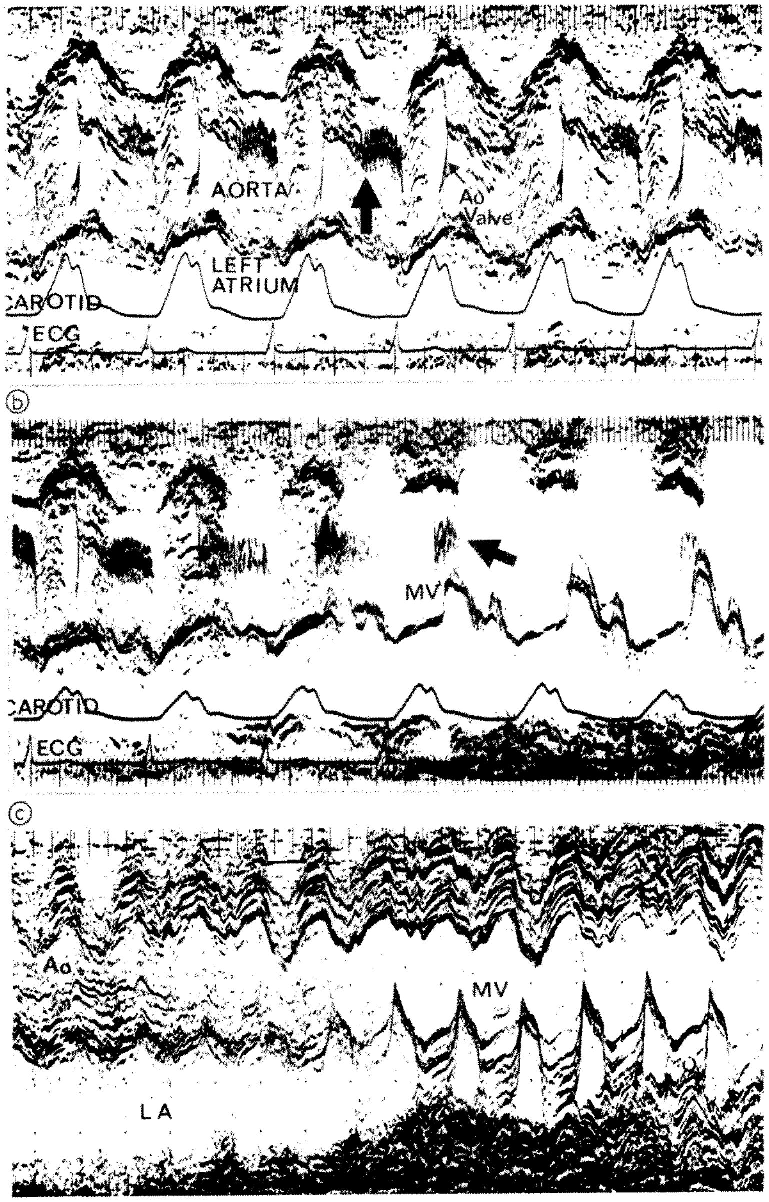

Fig. 2 *Abnormal echoes (arrows) present at level of aortic valve (a) and in left venticular outflow tract (b) with no discontinuity between the two areas. (c) Postoperative echocardiogram showing no abnormal echoes in the left ventricular outflow tract.*

and two weeks after heart surgery. A Smith-Kline Ekoline 20A ultrasonoscope with a 2·25 MHz 10 cm focused transducer was used. Records were made on a Cambridge photographic strip chart recorder. With the patient in the semi-recumbent position, several sweep recordings were made from the aortic valve to the apex in the long axis of the left ventricle.

Preoperative recordings (Fig. 2a and b) showed the normal box shaped configuration of the aortic valve echo with additional parallel echoes inside the box in systole. In diastole, an abnormal band of echoes showing high frequency oscillations was present both at the level of the valve (Fig. 2a) and in the left ventricular outflow tract in front of the anterior mitral leaflet (Fig. 2b). No discontinuity of the abnormal echoes was present as the transducer was swept between the two positions.

Postoperative examination showed no abnormal echoes in the left ventricular outflow tract (Fig. 2c).

Discussion

Abnormal echoes in the left ventricular outflow tract have been described in prolapsed aortic cusps (Lee *et al.*, 1974; Chandraratna *et al.*, 1975; Wray, 1975a) and bacterial endocarditis (Gramiak and Waag, 1975; Wray, 1975b; Yoshikawa *et al.*, 1976). A recent report attempted to distinguish the echocardiographic features between the two conditions (Chandraratna *et al.*, 1977). Our patient had both conditions, presumably as a result of bacterial endocarditis on a previously prolapsed cusp. Two important points are illustrated by the present case. Firstly, comparison of our patient's echocardiograms with published reports showed no distinguishing features from either prolapsed aortic cusp or valve vegetation. This shows the inability of this technique to differentiate the two conditions. Secondly, while abnormal echoes suggestive of valve vegetation may disappear after successful treatment of the infection (Chandraratna *et al.*, 1977), residual abnormal echoes may persist and thus can form no guide to medical therapy.

Operation was recommended in this patient on the grounds of progressive left ventricular dilatation. In retrospect there was also a real danger of the tenuously attached vegetation becoming detached, with forseeable consequences. This may be a point in favour of early valve replacement in patients with abnormal echoes in the left ventricular outflow tract, which persist after successful medical therapy for endocarditis.

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British Heart Journal, 1979, **41**, 121-124

An operation for anomalous origin of left coronary artery

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SUMMARY Successful surgical correction for anomalous origin of the left coronary artery from the pulmonary artery in a 4-year-old child is reported. An aortopulmonary fistula was created and a pericardial baffle was inserted within the pulmonary artery to connect the fistula to the ostium of the left coronary artery. The clinical, haemodynamic, and angiographic features of the anomaly are presented. The child's progress is satisfactory 17 months after the operation.

The majority of coronary artery malformations are anomalies in the site of origin—71 per cent in the necropsy series of Van Praagh (1973). In 26 per cent of cases the left coronary artery arose from the pulmonary artery. Thibert *et al.* (1973) pointed out that these anomalies should be defined as anomalous origin of the left coronary artery with drainage into the left posterior pulmonary sinus. Though these anomalies have been classified into 'adult' and 'infant' types (Augustsson *et al.*, 1962), there is overlap in the clinical presentation. Mortality is high in symptomatic infants having the so-called Bland-White-Garland syndrome (Billig, 1973). Though children above the age of 2 years have a favourable life expectation during childhood, the increasing morbidity of mitral regurgitation, progressive myocardial ischaemia, and congestive cardiac failure all militate against a normal life span and make surgical correction desirable.

A child with this anomaly has been treated surgically in this clinic by the creation of an aortopulmonary fistula and the insertion of a pericardial baffle within the pulmonary artery to connect the fistula to the ostium of the left coronary artery.

Case report

R.V., a baby girl was born by lower segment caesarean section for fetal distress at 38 weeks of gestation. The birthweight was 2·85 kg.

Tachypnoea was noticed at the age of 2 weeks, particularly after large feeds. The baby developed a respiratory infection at 3 months. The chest *x*-ray showed gross cardiomegaly. A clinical diagnosis of endocardial fibroelastosis was made. Cardiac catheterisation (Table) and left ventricular cineangiography disclosed a dilated and poorly contracting left ventricle. The right coronary artery was enlarged and tortuous. Mitral regurgitation was present. After treatment with digoxin her tachypnoea, pallor, and atrial gallop rhythm disappeared. She took feeds well and gained weight.

Table *Haemodynamic data*

Site	*Age 16 months*		*Age 3 years 9 months*	
	Pressure (mmHg)	*Oxygen saturation (%)*	*Pressure (mmHg)*	*Oxygen saturation (%)*
Right atrium		65	a 5, v 5 m 4	67
Right ventricle	35/7	61	25/4	65
Pulmonary artery	35/15	61	25/12 m 14	67
Left atrium	m 9	97·5	a 6 v 15 m 9	99
Left ventricle	70/12	97·5	100/10	99
Aorta			100/50	
			Qp = 2·5 l/min per m^2 Qs = 1·9 l/min per m^2 Pulmonary arteriolar resistance = 2 units	

Qp, pulmonary blood flow; Qs, systemic blood flow.

She was referred to this clinic at 16 months of age when she was asymptomatic and acyanotic. The heart was clinically enlarged. There was a grade 2/6 regurgitant systolic murmur at the apex and a 2/6 continuous murmur at the third left interspace. The liver was palpable 2 cm below the right costal margin. The chest *x*-ray showed moderate cardiomegaly. The electrocardiogram disclosed left ventricular hypertrophy, T inversion in V5 and V6, and left anterior hemiblock. QRS was 0·1 s in duration. She remained well on treatment with digoxin. The subsequent *x*-ray and electrocardiogram showed some improvement. The only symptom was dyspnoea on prolonged exertion.

She was recatheterised on 31 August 1976 (Table). Though oximetry showed no definite evidence of shunting dye dilution curves with injection into both left ventricle and aorta and sampling in the main pulmonary artery disclosed a left-to-right shunt. Anomalous origin of the left coronary artery draining into the pulmonary artery was diagnosed. The right coronary artery was dilated and tortuous. The left ventricle was dilated and contracted poorly. Grade 2 mitral regurgitation was present (Fig. 1). The day after the cardiac catheterisation she developed ventricular fibrillation but was resuscitated. In view of this event early operation was advised.

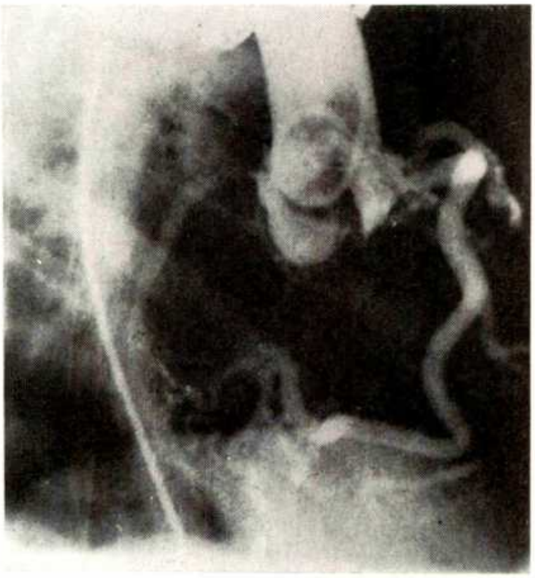

Fig. 1 *The anomalous left coronary artery shunting into the main pulmonary artery.*

OPERATION

The heart and great vessels were exposed through a median sternotomy. The great vessels were normal in size. A soft thrill was felt over the main pulmonary artery. The right coronary artery was large and tortuous. The left coronary artery was approximately 3·5 mm in diameter and divided early from a short main stem. It arose low down within the posterolateral pulmonary sinus. The thick-walled left ventricle contracted poorly.

The comparatively short length and small calibre of the left coronary artery before bifurcation contraindicated the insertion of a vein graft between the aorta and the left main coronary artery. The deep position of the aberrant coronary ostium within the lateral pulmonary sinus suggested that its removal from that site would have been both difficult and dangerous, and for this reason the left subclavian artery was not divided and turned down for such an anastomosis (see below).

Cardiopulmonary bypass was instituted with cannulation of the venae cavae and the ascending aorta. Perfusion cooling to 18°C with circulatory arrest for 60 minutes after exsanguination was employed. The main pulmonary artery was opened vertically. An aortopulmonary fistula 6 mm in diameter was created. A pericardial baffle was then inserted to cover the fistulous opening and was sutured along the posterior wall of the pulmonary artery and over the ostium of the left coronary artery. This ballooned up on releasing the aortic clamp and appeared to compromise the lumen of the main pulmonary artery. A diamond-shaped 'dacron' gusset was, therefore, inserted into the anterior wall of the pulmonary artery down to the level of the valve ring (Fig. 2).

POSTOPERATIVE PROGRESS

The postoperative recovery was uneventful. The child remains well and is active 17 months after operation. There is a faint thrill and a systolic murmur over the pulmonary artery. The electrocardiogram continued to show left anterior hemiblock. Echocardiography revealed a left ventricular end-diastolic dimension of 3·0 cm and a left ventricular end-systolic dimension of 2·3 cm compared with left ventricular end-diastolic of 3·6 cm and left ventricular end-systolic of 3·2 cm preoperatively. This suggests a reduction of left ventricular size and improved contractility. The systolic motion of the septum remains anterior because of left anterior hemiblock.

Discussion

The most satisfactory method of treatment of anomalous origin of the left coronary artery has not yet been defined. A number of techniques have been employed in infancy and childhood with varying degrees of success. These are (1) ligation of the anomalous left coronary artery at its pulmonary end (Sabiston *et al.*, 1960); (2) pulmonary artery constriction (Kittle *et al.*, 1955); (3) establishment of a two-coronary artery system by direct anastomosis or interposition of a 'dacron' tube, autogenous or allogenic saphenous vein graft (Neches *et al.*, 1974; Chiariello *et al.*, 1975; Venugopal and Subra-

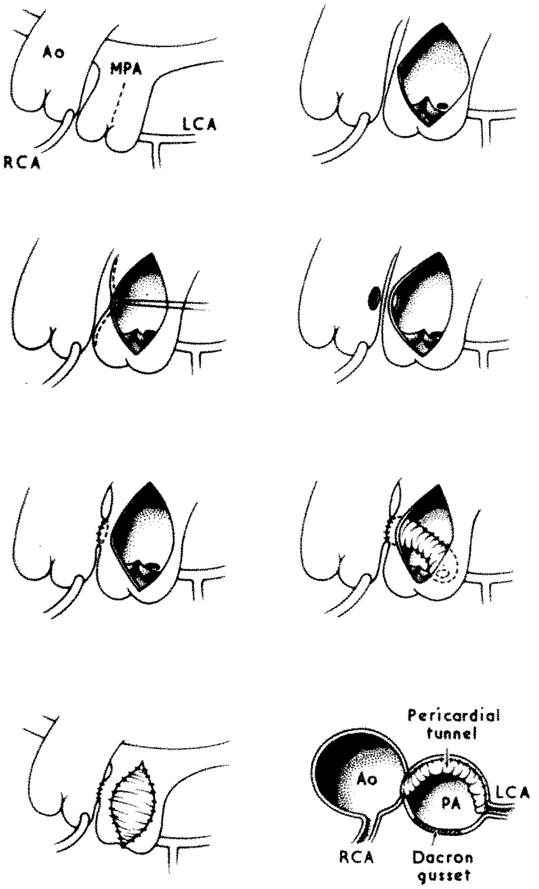

Fig. 2 *The steps of the operation.*

manian, 1975; Matsumoto *et al.*, 1976); (4) left subclavian artery—left coronary artery anatomosis (Meyer *et al.*, 1968; Pinsky *et al.*, 1976). Turina and coworkers (1974) considered left coronary artery ligation and left ventricular aneurysmectomy as adequate therapy in a 4-month-old infant. Though left coronary artery ligation stops the left-to-right shunt, it leaves the heart with a single coronary artery system and does little to improve left ventricular function. The mortality rate is high in infancy and the survivors in the infant group might have lived without surgical treatment (Likar *et al.*, 1966).

Stern and associates first reported the creation of an aortopulmonary fistula and insertion of an intrapulmonary baffle to connect the fistula to the ostium of the left coronary artery in 2 patients—a 4-month-old infant and a 2½-year-old girl. The infant died in the postoperative period. However, in the older child the conduit remained patent, the heart size decreased, and the ventricular contractility improved (H. Sloan, 1977, personal communication).

The creation of an aortopulmonary fistula for the treatment of anomalous left coronary artery was first suggested by Gasul and Loeffler in 1949, with the aim of increasing the blood flow to the left coronary artery from the pulmonary artery. Potts (1955) created an aortopulmonary fistula in 2 patients to increase the pulmonary artery pressure as well as the oxygen content of the blood within the left coronary artery. Perhaps the direction of blood flow from the left coronary artery into the pulmonary artery was not appreciated at this time and the serious disadvantage of increasing the workload of an already damaged left ventricle was noticed to offset any possible benefit of increasing the pulmonary artery oxygen saturation.

In addition to the creation of an aortopulmonary fistula it is necessary to insert a baffle within the pulmonary artery to isolate the coronary artery blood flow effectively. In the unfavourable anatomical situation where the main left coronary artery is short, as seen in our patient, the excision of the left coronary artery ostium with a flange of pulmonary artery may be difficult and direct aorto-left coronary artery anastomosis or the interposition of a saphenous vein graft may not be possible. In our patient the left coronary artery ostium lay deep within the sinus of the pulmonary artery and any attempt to detach the left coronary artery ostium with a flange of surrounding tissue would have been technically dangerous. Bulging of the baffle inside the pulmonary artery could lead to obstruction of pulmonary blood flow. This was minimised in our patient by 'dacron' patch arterioplasty of the main pulmonary artery.

Though the clinical, haemodynamic, and echocardiographic studies confirm the satisfactory outcome of this procedure in the short term, long-term assessment will be required for the proper evaluation of this procedure as a reliable method for the correction of this congenital abnormality.

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British Heart Journal, 1979, **41**, 125-127

Prosthetic valve endocarditis resulting from *Nocardia asteroides*

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SUMMARY *Nocardia asteroides* was isolated from the prosthetic valve of a 64-year-old woman who had died of endocarditis after aortic valve replacement. Multiple blood cultures had all been negative.

This organism is increasingly being recognised as a pathogen and is usually sensitive to sulphonamides. These should be tried in culture negative endocarditis unresponsive to standard therapy.

Case report

A 64-year-old woman had an aortic valve replacement with a Björk-Shiley prosthesis for severe calcific aortic valve disease. Immediate postoperative recovery was good and the prosthetic valve functioned well.

Six months after operation she experienced anorexia, weight loss, and night sweats. She was admitted to The General Hospital, Burton-on-Trent, 3 weeks after the onset of symptoms.

Examination revealed 3 splinter haemorrhages, no clubbing, clear prosthetic heart sounds, no hepatosplenomegaly, and normal urine. There was an intermittent pyrexia ranging from 36°C to 38·5°C. Haemoglobin 13·0 g/dl. Leucocytes 15 600 (80% neutrophils). Erythrocyte sedimentation rate 101 mm/h. Urea and electrolytes and liver function tests normal. Chest *x*-ray film showed cardiomegaly and pulmonary congestion but no evidence of focal infection.

Blood cultures were sterile, but in view of the possibility of an infected prosthesis she was started on gentamicin and ampicillin. Despite this therapy, her pyrexia persisted, the erythrocyte sedimentation rate remained high, and she became progressively more anaemic.

Three weeks after admission, she developed aortic systolic and diastolic murmurs and was transferred to Dudley Road Hospital, Birmingham, under the care of Dr J. Mackinnon.

On examination she was anaemic with splinter haemorrhages, collapsing pulse, cardiomegaly, and murmurs of aortic regurgitation. Blood pressure was 120/45 mmHg. She had a moderate left hemiplegia and bilateral papilloedema.

Haemoglobin 7·9 g/dl. Leucocytes 9000. Blood cultures negative. She rapidly deteriorated, became comatose, and died.

NECROPSY (S. M. Abraham)

This showed left ventricular hypertrophy and fibrinous covering of the prosthetic valve on which small vegetations were present. A suture had become detached, giving rise to paraprosthetic leak (Fig. 1).

There was splenomegaly and extensive haemorrhage into the right cerebral hemisphere (Fig. 2). A cystic lesion was present in the left kidney.

Culture of the vegetations yielded colonies of Gram-positive branching filaments identified as *Nocardia asteroides*. The organism was resistant to both gentamicin and ampicillin but sensitive to sulphonamides.

Histology of the vegetations and of the kidney showed the same organism but it was not seen on histology of the brain or spleen.

A strongly positive precipitin reaction of the patient's serum, taken before death, was obtained with micropolysporon antigen (farmer's lung reaction) due to cross-reacting antibodies and the precipitin test for *Nocardia asteroides* was also strongly positive.

Comment

Infection of a prosthetic heart valve is a well-recognised complication occurring either shortly after operation or several months later (Dismukes *et al.*, 1973). The spectrum of infecting organisms differs slightly from the usual in infective endo-

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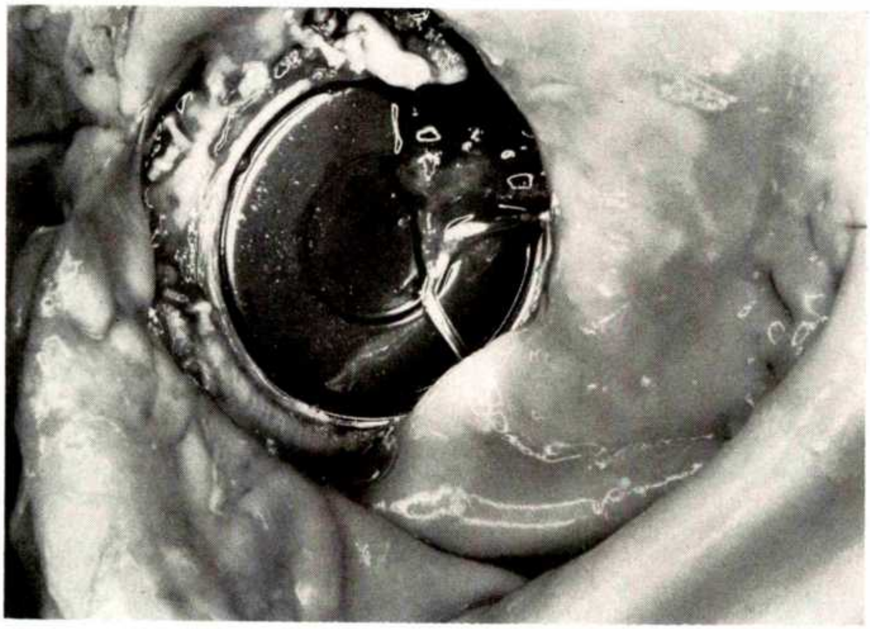

Fig. 1 *Björk-Shiley prosthesis showing vegetations.*

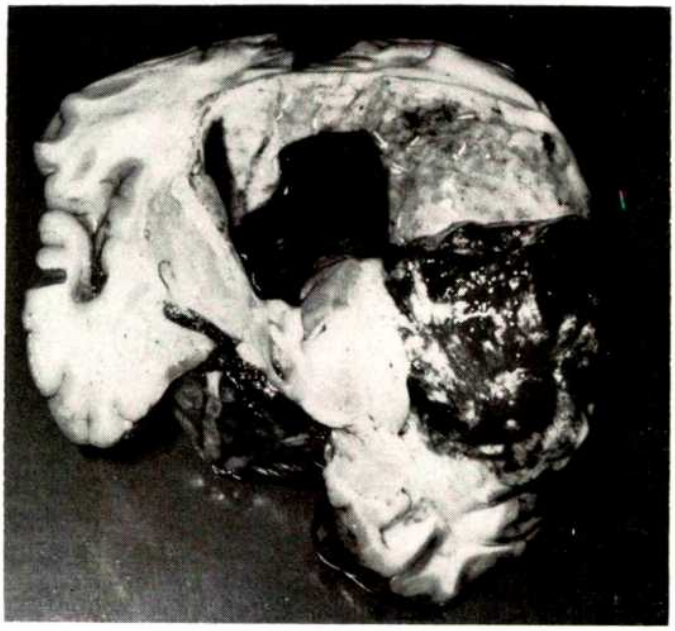

Fig. 2 *Brain—showing extensive cerebra haemorrhage extending into the ventricles.*

carditis with staphylococci predominating but with a proportion of Gram-negative or fungal organisms (Slaughter *et al.*, 1973).

Nocardia asteroides, a Gram-positive fungus, is now increasingly recognised as a pathogen in immunosuppressed patients and those with lymphoreticular disorders, and pulmonary involvement occurs in over 70 per cent of patients (Palmer *et al.*, 1974). It has only been reported once previously as a cause of infection on a prosthetic valve

(Vlachakis *et al.,* 1973). In the present case, and in the one previously reported, there was no clinical or radiological pulmonary involvement. Blood cultures were negative in both cases but the organism has been isolated from skin lesions (which were not present in our patient).

Despite the fact that widespread dissemination of the organism, particularly to the central nervous system, is common, treatment of systemic nocardiasis with sulphonamides has been very successful even in patients with severe immunological impairment (Palmer *et al.,* 1974).

Although definitive diagnosis depends upon isolation of the organism, this may be difficult as blood cultures are frequently negative. Precipitin tests may be helpful and a trial of sulphonamides in a patient with the clinical features of endocarditis, with negative blood cultures, unresponsive to standard therapy, may be life-saving.

We thank Dr J. Mackinnon for permission to publish the case and Dr S. M. Abraham for the necropsy and histology reports.

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Requests for reprints to Dr R. H. Falk, Cardiac Department, King's College Hospital, London SE5.

Notices

British Heart Journal, 1979, **41**, 128

Second European Balloon Pump Congress

This congress will be held in Vienna on 5-7 June 1979.

Abstracts in English are invited and the deadline for their receipt is 1 February 1979. Deadline for registration is 1 March 1979.

For further information write to: Prof. Dr F. Kaindl, Kardiologische Universitäts-Klinik, Garnisongasse 13, A 1090 Wien, Austria.

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For further information, apply to: Professor Dr F. L. Meyler, Department of Cardiology, University Hospital, Catharijnesingel 101, 3500 CG Utrecht, The Netherlands.

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A symposium on paediatric echocardiography will be held in the Department of Paediatric Cardiology, University Hospital, Lund, on 6-9 June 1979.

For information apply to: the Secretariat, Department of Paediatrics, University Hospital, S-221 85 Lund, Sweden.

Non-invasive Imaging in Medicine

A symposium on non-invasive imaging in medicine related to heart, liver, and pancreas will be held on 6-9 June 1979 at University Hospital, Lund, Sweden.

For information, apply to: the Secretariat, Department of Cardiology, University Hospital S-221 85 Lund, Sweden.

Non-invasive Techniques in Cardiology

A three-day symposium on non-invasive techniques in cardiology sponsored by the British Heart Foundation will be held in London from 26-28 June 1979.

Reservation forms are available from Conference Services Ltd, 43 Charles Street, London W1.

International Symposium on Pulmonary Circulation

An international symposium, pulmonary circulation III, will be held in Prague, Czechoslovakia, 2-4 July 1979.

Information can be obtained from J. E. Purkyně, the Czechoslovak Medical Society, International Symposium Pulmonary Circulation III, 120 26 Prague 2, Sokolská 31, Czechoslovakia.

XVth International Congress of Therapeutics

The XVth International Congress of Therapeutics will be held at the Palais des Académies in Brussels from 5 to 9 September 1979.

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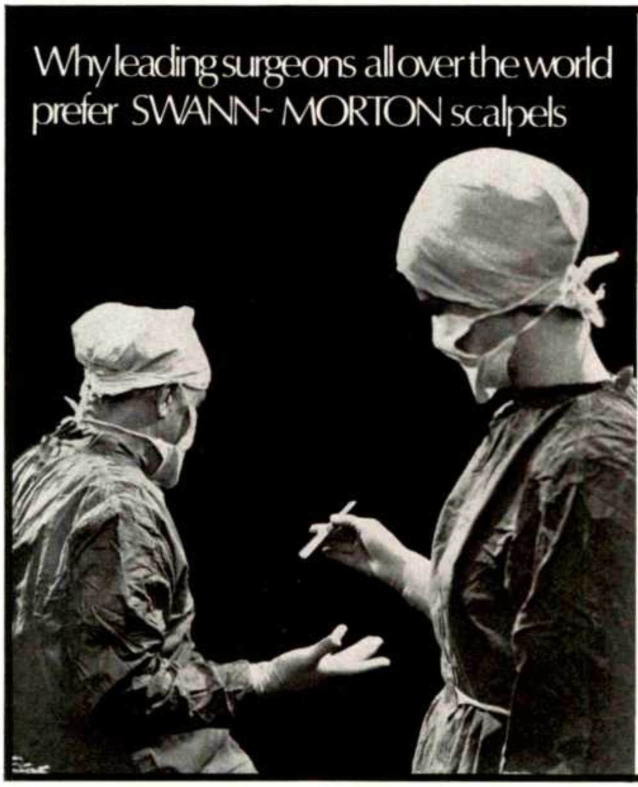
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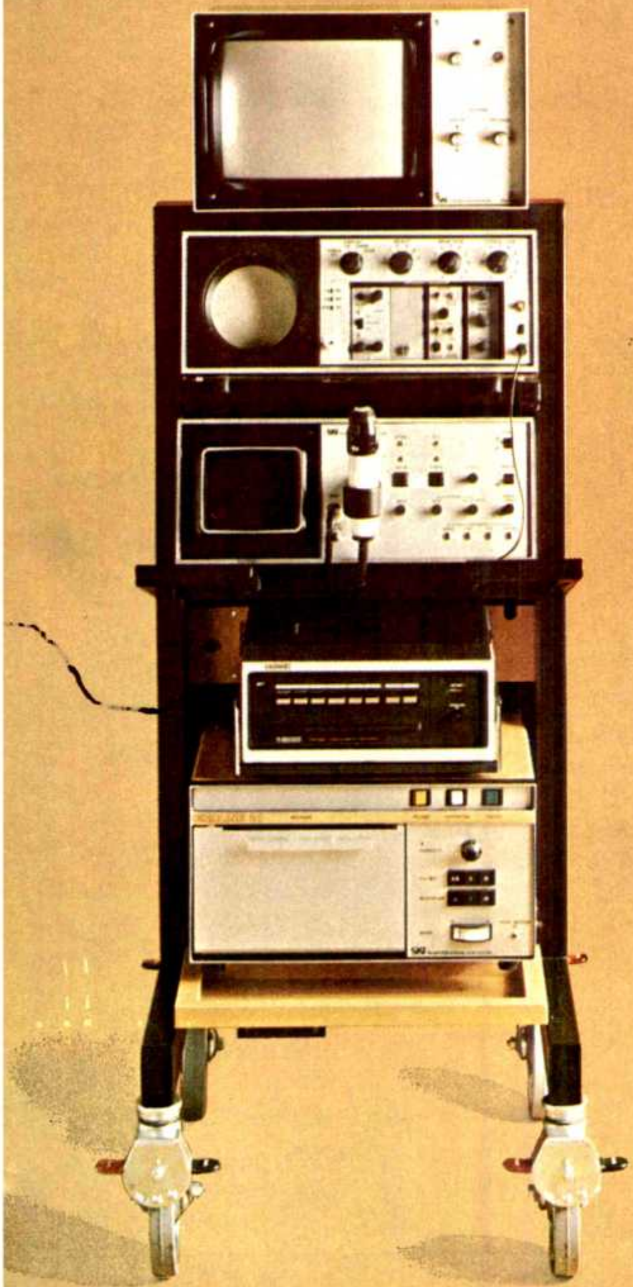

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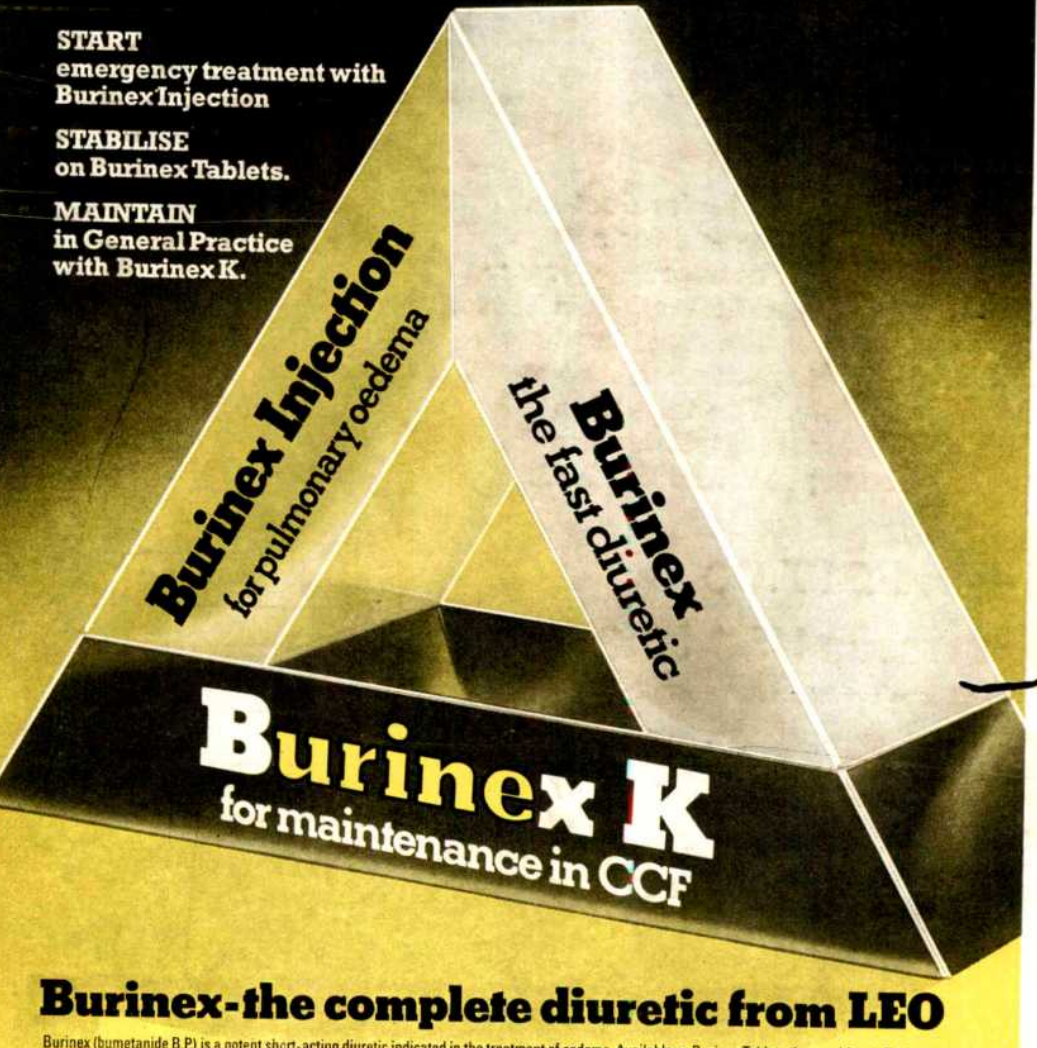

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Disposition of the sinus node in left-sided juxtaposition of the atrial appendages *S. Yen Ho, J. L. Monro and R. H. Anderson* 129

Surgical treatment of ventricular septal defect in infancy. Primary repair versus banding of pulmonary artery and later repair *K. McNicholas, M. de Leval, J. Stark, J. F. N. Taylor, and F. J. Macartney* 133

Echocardiographic and exercise evaluation of results of mitral valvotomy operations *M. F. Shiu, A. Crowther, B. S. Jenkins, and M. M. Webb-Peploe* 139

Assessment of left-to-right shunt and left ventricular function in isolated ventricular septal defect. Echocardiographic study *M. Ahmad and K. A. Hallidie-Smith* 147

Fixed subaortic stenosis. Value of echocardiography for diagnosis and differentiation between various types *F. J. Ten Cate, W. G. Van Dorp, P. G. Hugenholtz, and J. Roelandt* 159

Management of unstable angina at rest by verapamil. A double-blind cross-over study in coronary care unit *O. Parodi, A. Maseri, and I. Simonetti* 167

Effects of tocainide on left ventricular performance at rest and during acute alterations in heart rate and systemic arterial pressure. An echocardiographic study *W. F. Ryan and J. S. Karliner* 176

Observations on haemodynamic effects of mexiletine *N. P. S. Campbell, S. A. Zaidi, A. A. J. Adgey, G. C. Patterson, and J. F. Pantridge* 182

Haemodynamic effects of sodium nitroprusside in 21 subjects with congestive heart failure *S. A. Lukes, C. A. Romero, Jr., and L. Resnekov* 187

Haemodynamic adaptation at rest and during exercise to long-term antihypertensive treatment with combined alpha- and beta-adrenoreceptor blockade by labetalol *G. Koch* 192

Non-invasive assessment of left ventricular response to Valsalva manoeuvre in normal and diabetic subjects using praecordial accelerocardiography *L. Hume, D. J. Ewing, I. W. Campbell, S. R. Reuben, and B. F. Clarke* 199

Pre- and postoperative left ventricular contractile function in patients with aortic valve disease *H. P. Krayenbuehl, M. Turina, O. M. Hess, M. Rothlin, and A. Senning* 204

Electrocardiographic changes resembling myocardial ischaemia in asymptomatic men with normal coronary arteriograms *P. Taggart, M. Carruthers, S. Joseph, H. B. Kelly, J. Marcomichelakis, D. Noble, G. O'Neill, and W. Somerville* 214

Early clinical experience with the Hancock porcine xenograft valve prosthesis *C. T. M. Sang, J. Wallwork, H. C. Miller, A. H. Kitchin, K. G. Davidson, and P. K. Caves* 226

Left ventricular ejection power in coronary artery disease during atrial pacing *K. Hagemann, J. Meyer, R. v. Essen, Winifried Krebs, and S. Effert* 231

Unusual angiographic appearances of the left ventricle in 2 cases of Pompe's disease (glycogenosis type II) *D. F. Dickinson, W. T. Houlsby, and J. L. Wilkinson* 238

Case reports

Double outlet right ventricle with subvalvular aortic stenosis *B. D. Thanapoulos, Ira W. Dubrow, Elizabeth A. Fisher, and A. R. Hastreiter* 241

Effects of propranolol in a case of orthostatic hypotension *G. Brevetti, M. Chiariello, G. Lavecchia, and F. Rengo* 245

Corrected transposition of great vessels and Ebstein's anomaly of tricuspid valve. Echocardiographic findings *J. G. Henry, S. Gordon, and G. C. Timmis* 249

Correspondence 253

Notices 256

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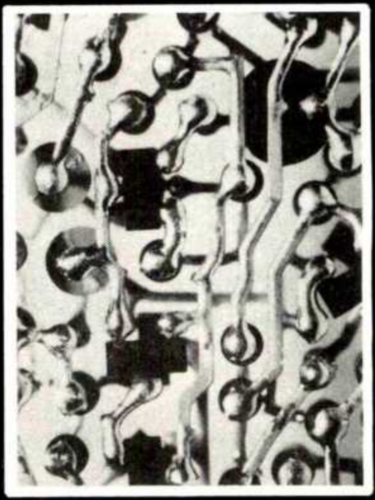

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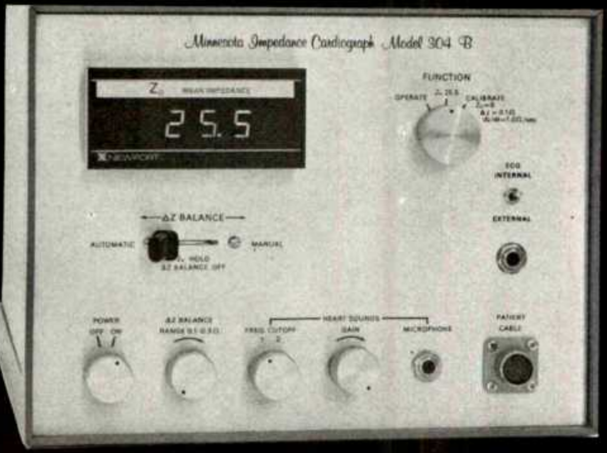

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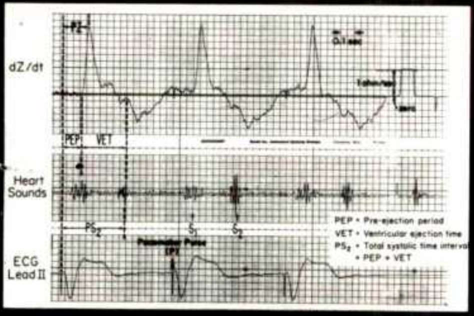
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ECG Lead II
PEP
VET
PS₂
S₁
S₂
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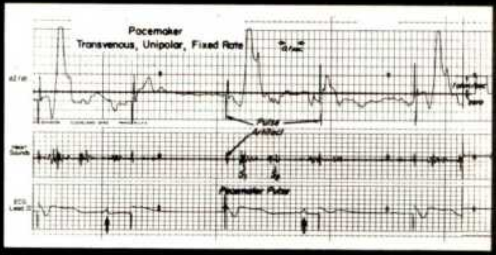
PEP = Pre-ejection period
VET = Ventricular ejection time
PS₂ = Total systolic time interval = PEP + VET

Fig. 1. A normal functioning pacemaker and a normal functioning heart. Note the systolic time intervals. PEP is longer than normal, all other parameters similar to the normal heart.



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References: 1. Med. J. Aust. (1973). *1*:1223.
2. JAMA (1972). *222*:676.
3. New Zealand J. Med. (1972). *76*:12.

Prescribing Information

Presentations: Tasteless and odourless granules of colestipol hydrochloride. *Uses:* Adjunctive therapy to diet for treatment of hypercholesterolaemia, particularly Frederickson Type II. *Dosage and Administration:* Always mix with water or other fluids before ingesting. Oral total daily dosage for adult 15–30 grams. Take in divided doses 2–4 times daily. *Contraindications:* Hypersensitivity to colestipol. *Precautions, Warnings:* Not to be taken in dry form. Colestid may interfere with absorption of some drugs (e.g. penicillin G, tetracycline, chlorothiazide). Safety for use in pregnant women or children not established. *Package Quantities:* 30 x 5 g sachets; 250 g bottle. Each sachet or scoopful contains 5 g colestipol hydrochloride. *Further Information:* Colestid is not absorbed. It binds bile acids causing further cholesterol conversion to bile acids thus lowering serum cholesterol levels. *Basic NHS Costs:* 30 x 5 g sachets £8.90. 250 g bottle £13.76. Product Licence Nos. PL 0032/0055. PL 0032/0057. *Full Product information is available on request.*

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[1] Data on file awaiting publication.

British Heart Journal, 1979, **41**, 129-132

Disposition of the sinus node in left-sided juxtaposition of the atrial appendages

S. YEN HO, JAMES L. MONRO, AND ROBERT H. ANDERSON[1]

From the Department of Paediatrics, Cardiothoracic Institute, Brompton Hospital, London; and Wessex Cardiothoracic Surgical Centre, Southampton

SUMMARY In view of the complex cardiac anomalies frequently associated with left-sided juxtaposition of the atrial appendages the disposition of the sinus node has been studied in 6 of these hearts. While the sulcus terminalis still provides a landmark to the position of the node, the nodes were in an anterior position in all 5 hearts with complete juxtaposition, 2 being inferior to the crista terminalis. The node was in a more normal, lateral position in the sixth case with partial juxtaposition.

The disposition of the sinus node originally described by Keith and Flack (1907) has since been well investigated (for example Davies, 1942; Hudson, 1960; Challice, 1966; James *et al.*, 1966; Truex *et al.*, 1967; Lev, 1968; James, 1970; Anderson *et al.*, 1979). As the right atrium and its appendage are common sites for manipulation, placement of sutures, and cannulation in cardiac surgery, it is imperative that the areas bearing the sinuatrial node and its arterial supply be avoided.

To the best of our knowledge the disposition of the sinuatrial node has not yet been ascertained in hearts with juxtaposed atrial appendages. Normally each atrial appendage lies to one side of the great arteries. The term 'juxtaposition of the atrial appendages' was coined by Dixon (1954) to describe the condition whereby both atrial appendages were adjacent to each other and lie to the same side of the great arteries. As juxtaposition is often associated with complex cardiac malformations (Melhuish and Van Praagh, 1968) requiring correction or palliation for continuing life, precise knowledge of the location of the sinus node in the malformation is of paramount importance. For instance, correction of ventriculoarterial discordance, a commonly associated anomaly with juxtaposition (Melhuish and Van Praagh, 1968; Rosenquist *et al.*, 1974; Allwork *et al.*, 1977), by Mustard's repair would involve considerable atrial manipulation. A similar situation would arise if tricuspid atresia, another frequent association (Melhuish and Van Praagh, 1968), was present and a conduit was attached to the right atrium in attempting correction (Fontan and Baudet, 1971).

For these reasons we have ascertained the disposition of the sinus node in 6 patients with left-sided juxtaposition of the atrial appendages.

Subjects and methods

Six hearts with both right and left atrial appendages to the left of the great arteries were available for

Table *Postmortem diagnoses of 6 specimens with left-sided juxtaposition*

Case no.	*Segmental arrangement Situs—AV connection—VA connection*	*Associated cardiac anomalies*
1	Solitus-absent right connection—discordant (univentricular heart LV type)	Secundum ASD; right sided OC; persistent LSVC; coarctation and tubular hypoplasia
2	Solitus-concordant-single aortic trunk	Secundum ASD, straddling TV; pulmonary atresia; persistent LSVC
3	Solitus-concordant-discordant	ASD; VSD (subaortic), pulmonary stenosis; PDA, right aortic arch
4	Solitus-concordant-DORV—with right-sided aorta	ASD, VSD (extensive)
5	Solitus-concordant-DORV—with left-sided aorta	PFO; VSD (posterior) pulmonary outflow stenosis
6	Solitus-concordant-discordant	PFO: VSD (extensive); tricuspid atresia

ASD, atrial septal defect; AV, atrioventricular; LV, left ventricular; OC, outlet chamber; PDA, persistent ductus arteriosus; PFO, patent foramen ovale; TV, tricuspid valve; VA, ventriculoarterial; VSD, ventricular septal defect; LSVC, left superior vena cava.

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[1] R.H.A. is supported by the Joseph Levy Foundation together with the British Heart Foundation.

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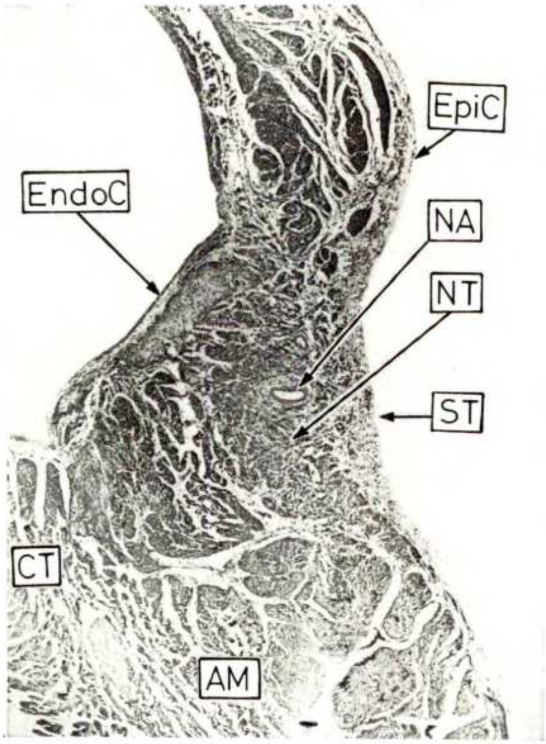
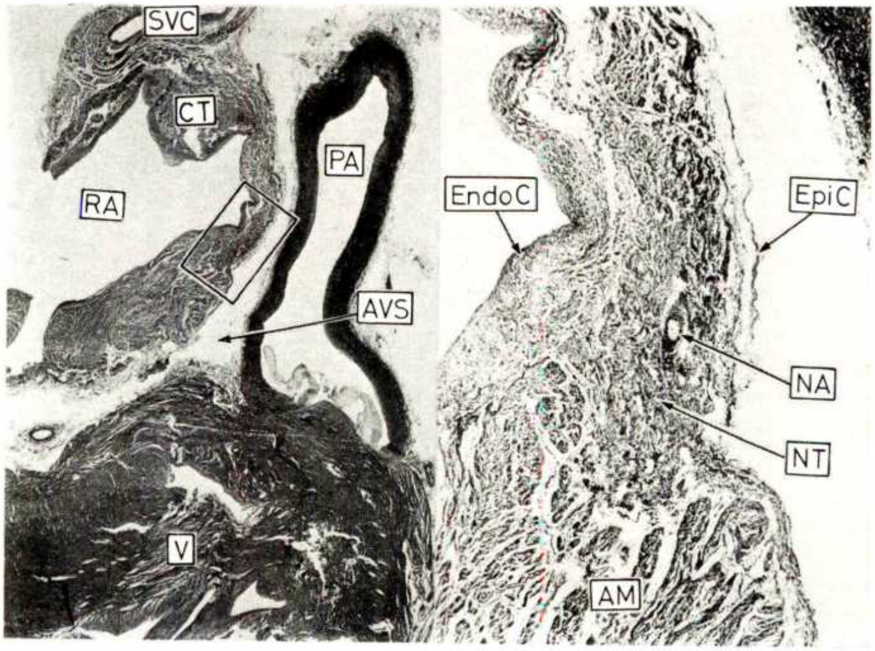


Fig. 1 *Photomicrograph of a longitudinal section through the atrio-caval junction of a normal heart. Nodal tissue (NT) is related to a nodal artery (NA). The sinus node is subepicardial and located in the sulcus terminalis (ST). AM, atrial myocardium; CT, crista terminalis; EndoC, endocardium; EpiC, epicardium. (Trichrome stain. × 46.)*

Fig. 2 *The photomicrograph on the left is a section through specimen 1. The sinus node is inferior to the crista terminalis and towards the atrioventricular sulcus. The rectangle marks the area shown on the right photomicrograph. The sinus node is related to a nodal artery. AVS, atrioventricular sulcus; CT, crista terminalis; PA, pulmonary artery; RA, right atrium; SVC, superior vena cava; V, ventricle; AM, atrial myocardium; EndoC, endocardium; EpiC, epicardium; NA, nodal artery; NT, nodal tissue. (Elastic van Gieson stain. × 3·4 and × 23.)*



study from the Brompton Hospital collection. One of these had partial juxtaposition in that though a large part of the right atrial appendage was juxtaposed to the left, a small portion remained to the right of the great arteries. Two of the hearts were processed and embedded in paraffin wax *in toto*. Each block was then serially sectioned in a sagittal plane from right to left at 10 μ thickness. Every 25th section was mounted and stained using Masson's trichrome technique. Additional sections were stained as deemed necessary after initial examination. After locating the sinus node in these 2 hearts, strips of atrial wall expected to bear the sinus node were excised from the third to fifth hearts and prepared as above. The entire right and left atria were removed in a single block from the sixth heart, processed, and sectioned transversely.

Results

The complex associated malformations in the hearts studied are shown in the Table.

The sinus node was identified in all cases. In terms of histology the structure of the nodes was no different from those of normal hearts which we studied in another investigation (Anderson *et al.*, 1979, Fig. 1). However, the position of the node showed considerable variation, both from the normal and among the hearts studied. The first 2 specimens had persistent left superior venae cavae but no specialised tissue was seen in its vicinity. The sinuatrial node in these 2 cases was seated in the anterior wall of the right atrium in the dip of the atrioventricular sulcus (Fig. 2 and 3). The nodes were nearly spindle-shaped and supplied by a small central artery which was a branch of an anterior atrial artery. There was no evidence of a branch to the sinuatrial junction.

The third and fourth specimens also had spindle-shaped sinuatrial nodes but they were located anteriorly at the sinuatrial junction (Fig. 3). The node in the fourth specimen was somewhat dispersed and the matrix was very fibrous. Also, the vicinity of this node was haemorrhagic. The nodal arteries were eccentric in relation to the nodes.

The node in the fifth specimen was on the anterior atrial wall, inferior to the sinuatrial junction (Fig. 3). It was shaped like a flattened spindle and located subepicardially. The matrix was mainly fibrous and some adipose tissue was also seen. The nodal artery was large.

The sixth case, which had partial juxtaposition, had the sinuatrial node in a more 'normal' position. It nestled in the sulcus terminalis between the 'bud' of the right atrium and the superior vena cava and stretched across to the lateral side (Fig. 3). The nodal artery was large and penetrated the node centrally after crossing the front of the right atrium.

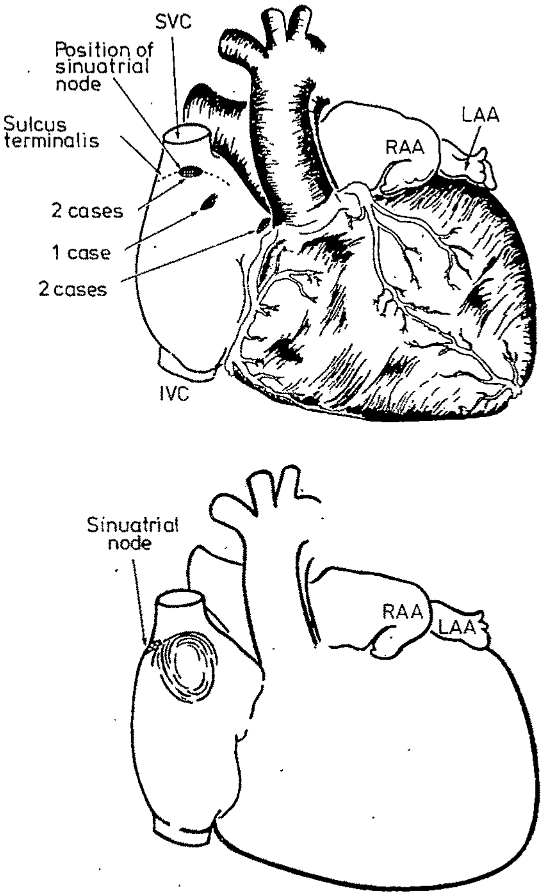


Fig. 3 *Diagrams to show the positions of the sinus nodes in left-sided juxtaposition of the atrial appendages. The upper diagram shows the nodes in 5 cases of complete juxtaposition while the lower diagram shows the node in partial juxtaposition. In the latter case the node is in a more lateral position behind the 'bud' of the right atrial appendage. IVC, inferior vena cava; LAA, left atrial appendage; RAA, right atrial appendage; SVC, superior vena cava.*

Discussion

The sinuatrial nodes in the abnormal hearts did not differ histologically from the normal (Anderson *et al.*, 1979). Their position did show more variation. In the normal, the node usually occupies a lateral position in the sulcus terminalis. In the hearts with juxtaposition, the node was more anterior, usually still being found in the sulcus terminalis but being located in an unusually low position in 2 cases. In the latter hearts the node was found on the dip of the anterior atrial wall towards the atrioventricular sulcus. The nodal artery in these cases was an anterior atrial branch of the artery which also supplied the roof of the left atrium. Retrospective study of the electrocardiogram showed that these 2 cases had a high P wave vector of +90° while the other cases were well within normal limits. The sixth case, with partial juxtaposition, showed a more normal position of the node behind the bud of the right atrial appendage on the right, being laterally located within the sulcus terminalis.

Contrary to Rosenquist *et al.* (1974), who commented that the crista terminalis was absent in their cases of partial juxtaposition, being invaginated into the juxtaposed right atrial appendage, the crista in all our cases was observed in its usual course and gave rise to pectinate muscles on the anterior atrial wall. As in the normal, its position was marked externally by the sulcus terminalis and consequently continues to provide a landmark to nodal position. As indicated, however, in 2 cases the node was inferior to the crista terminalis. None the less, in view of the consistent anterior location of the sinus node in complete juxtaposition of the atrial appendages together with the fact that the arterial supply is from an anterior artery, it is desirable to avoid this area in surgery, particularly in Fontan's procedure. The 2 inferior nodes appear to be located in a relatively safe area.

Although it is now possible to diagnose juxtaposition by cardiac catheterisation and angiography (Ellis and Jameson, 1963; Hunter *et al.*, 1973; Deutsch *et al.*, 1974) only one of our cases was diagnosed as such before operation. All our cases with left-sided juxtaposition were associated with severe ventricular and infundibulo-truncal malformations (Table) (Melhuish and Van Praagh, 1968; Anderson *et al.*, 1976). Early diagnosis should draw the surgeon's attention to these anomalies, particularly the high probability of either presence of tricuspid atresia or hypoplasia of the right ventricle.

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British Heart Journal, 1979, **41**, 133-138

Surgical treatment of ventricular septal defect in infancy

Primary repair versus banding of pulmonary artery and later repair[1]

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From the Thoracic Unit, The Hospital for Sick Children, Great Ormond Street, London

SUMMARY Results of primary closure of ventricular septal defects are compared with those of two-stage repair, with banding of the pulmonary artery followed by debanding and closure.

Apart from the high incidence of unsatisfactory results after banding and a significant morbidity with the two-stage approach, the mortality for primary repair (2·4%) is considerably lower than that achieved with the staged repair (19·3%). Primary repair of ventricular septal defect is advocated for infants resistant to maximal medical treatment. A more flexible policy is adopted for patients with multiple ventricular septal defects and those with associated anomalies.

Intractable congestive heart failure, failure to thrive, and repeated chest infections are the main indications for surgical treatment of ventricular septal defect with a large left-to-right shunt during the first year of life. Raised pulmonary vascular resistance alone is rarely an indication for surgical treatment of ventricular septal defect before the age of 1 year. The increasing number of encouraging reports on the results of primary closure of ventricular septal defect in infancy (de Leval *et al.*, 1974; Johnson *et al.*, 1974; Barratt-Boyes *et al.*, 1976; Kirklin *et al.*, 1976; Subramanian, 1976; Rein *et al.*, 1977; Sigmann *et al.*, 1977) is certainly in favour of the one-stage rather than two-stage repair (pulmonary artery banding, followed by closure of ventricular septal defect and debanding at a second stage). It is, however, of some concern that comparable data from the two management programmes are not available. A randomised trial of both approaches from the outset would have been ideal, but the initial reports of primary closure have been so favourable that many would regard a trial at this stage as unjustifiable. Because of differences in patient material and surgical practice, comparison of the two approaches from different centres, or from one centre during different eras, is of limited value. In an attempt to make a more valid comparison we have reviewed our experience at The Hospital for Sick Children, Great Ormond Street, London, with these two approaches during the same period, January 1971 to December 1976.

Clinical material

In the 6-year period, 1971 to 1976, 24 infants (i.e. children less than 12 months of age) with ventricular septal defect as their dominant lesion have undergone pulmonary artery banding (group 1). Their ages at time of operation ranged from 6 days to 7 months (mean 3·0 months), and their weights from 2·0 to 6·1 kg (mean 3·8 kg) (Fig. 1 and 2).

During the same period, closure of ventricular septal defect was undertaken in 41 infants aged 1 to 11 months (mean 6·2 months), weighing 2·5 to 7·5 kg (mean 4·8 kg) (Fig. 1 and 2) (group 2). The cardiac lesions in the two groups are listed in Table 1. Under single high ventricular septal defect, we have included ventricular septal defects in the region of the membranous septum and/or the infundibular septum. Several patients in that group had an atrial septal defect and/or a persistent ductus

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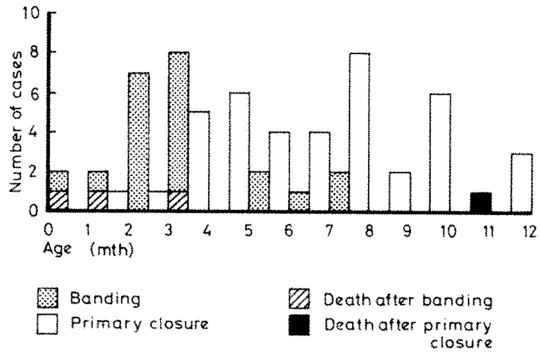

Fig. 1 *Banding versus primary repair. Age distribution and hospital mortality.*

Table 1 *Primary operation in infants with ventricular septal defect: banding or primary closure*

Lesion	*Banding*		*Primary closure*	
	No.	%	*No.*	%
Single high ventricular septal defect	15	62·5	39	95
Multiple ventricular septal defects	2	8·3	2	5
Ventricular septal defect + coarctation	7	29·2		
Total	24	100	41	100

arteriosus in addition. Under ventricular septal defect and coarctation of the aorta, we have included patients with single (4 patients) or multiple septal defects (3 patients). All these patients were submitted to an identical intensive medical regimen, consisting of full digitalisation, diuretics, nasogastric tube feeding in many cases, and assisted ventilation in some. Antibiotic therapy was used only when an infection was present. In the infants with a tight coarctation, this was resected as an emergency before the trial period of medical treatment. Preoperative investigations in all patients included a full cardiac catheterisation with selective angiocardiography. This included a left ventriculogram with the patient positioned to profile the interventricular septum in order to determine the number and location of the ventricular septal defects. All the patients had a pulmonary/systemic flow ratio greater than 2·5:1. The decision to band or to proceed with intracardiac repair was not randomised. In 6 infants early in this series, closure of the ventricular septal defect was performed after failure of banding to alleviate cardiac failure. Later, some patients who required urgent operation underwent pulmonary artery banding, as our limited facilities precluded open-heart repair at short notice. For patients with coarctation of the aorta, banding was carried out at the time of operation for correction of coarctation when the left-to-right shunt at ventricular level was considered to be a major component in inducing the heart failure.

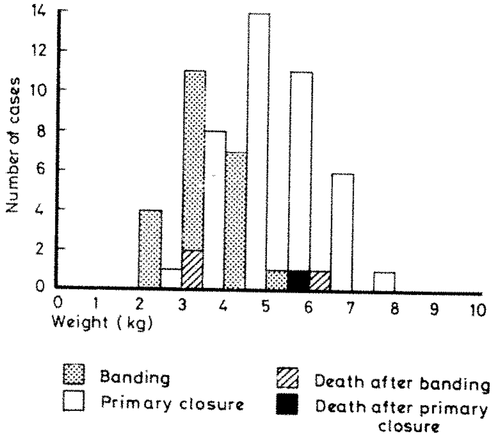

Fig. 2 *Banding versus primary repair. Weight distribution and hospital mortality.*

In order to assess the cumulative morbidity and mortality of a two-stage repair, we have also reviewed our results of intracardiac repair after previous banding (group 3). The repair in this group of patients was performed during the same period, 1971 to 1976. There were 58 patients aged between 2 and 9 years (mean 5·4 years). All had been banded in infancy (10 days to 10 months) (mean 5·2 months). There were 52 single ventricular septal defects and 6 multiple ventricular septal defects (Table 2). Patients with a failed banding who also underwent closure during infancy are not included in this group.

SURGICAL TECHNIQUES AND RESULTS IN 3 GROUPS

(*1*) *Pulmonary artery banding*

Our technique of banding the pulmonary artery has

Table 2 *Closure of ventricular septal defect + debanding*

Lesion	*Patients*	*Mortality*	
		No.	%
Single high ventricular septal defect	47	2	4·2
Midseptal ventricular septal defect	2	0	0
Apical ventricular septal defect	3	0	0
Multiple ventricular septal defects	6	2	33·3
Total	58	4	6·8

been described previously (Stark *et al.*, 1969). There were 2 operative deaths in this group (mortality rate of 8·3%), one in a 1-month-old infant and the other in a 6-day-old baby; the latter patient also had a coarctation of the aorta which was resected. Pulmonary artery banding was not effective in controlling congestive heart failure in 8 patients (33·3%). These patients remained in congestive heart failure despite a diminution in the pulmonary artery pressure, often after a short period of improvement. One patient died 10 weeks after operation in heart failure. In addition, he had a tracheo-oesophageal fistula repaired and a ventriculoatrial shunt constructed for hydrocephalus. One infant was banded again successfully and the other 6 patients underwent closure of the ventricular septal defect and debanding of the pulmonary artery. These 6 patients are also included in the group who underwent closure of ventricular septal defect in infancy. The mortality rate for the first group is, therefore, 3 patients out of 24 (12·5%).

(2) *Closure of ventricular septal defect in infancy*
Forty-one infants underwent closure of ventricular septal defect in infancy between 1971 and 1976. Conventional cardiopulmonary bypass with moderate hypothermia was used in 30 patients (73%). The technique of deep hypothermia and total circulatory arrest was used in 11 patients (27%). The surgical approach is summarised in Table 3, which indicates our preference for closure of ventricular septal defect through the right atrium. The transventricular approach was used mainly in the beginning of the series before we had acquired more experience with the transatrial closure. At the present time, the majority of ventricular septal defects are closed through the right atrium. The defects were closed with a prosthetic patch in 37 patients and by direct suture in 4 patients. When the defect was closed through the right atrium, the septal and anterior leaflets of the tricuspid valve were retracted but not detached. Interrupted or running sutures were employed. An apical left ventriculotomy was used in 2 patients with a defect in the lower part of the muscular septum (Singh *et al.*, 1977). The ventricular septal defect was closed through a short right ventriculotomy in 14 patients. When a persistent ductus arteriosus was present, this was dissected intrapericardially and doubly ligated before cannulating the ascending aorta. The ductus arteriosus was routinely dissected in all patients whose operations were done under deep hypothermia and circulatory arrest when there was pulmonary hypertension, even if the investigation had failed to demonstrate its patency. In these patients, we think that an aortogram does not reliably rule out a small persistent ductus arteriosus that would be a source of air embolus when the circulation is arrested and the right heart opened. All defects in the atrial septum, no matter how small, were routinely closed to prevent any right-to-left shunts in the postoperative period. The postoperative complications are listed in Table 4. Arrhythmias in the immediate postoperative period were relatively frequent (19%) but were all temporary. One patient required reoperation for wound infection and another patient for a residual ventricular septal defect. The latter patient did well after the second closure of the ventricular septal defect; one suture had cut through the tricuspid valve and the patient had a large shunt from the left ventricle to the right atrium. A cardiac arrest occurred 36 hours after operation in another patient. After resuscitation he had convulsions and his subsequent development indicates major cerebral damage. This patient has also remained in congestive heart failure. A repeat cardiac catheterisation showed a significant shunt between the left ventricle and the right atrium. A second patient had convulsions, but these ceased and there was no evidence of permanent brain damage.

There was 1 hospital death (2·4%) and 1 late death. The hospital death occurred in an 11-month-old infant who sustained a sudden cardiac arrest 24 hours after operation. The ventricular septal defect was securely closed and the reason for his sudden death remains unexplained. The late death was not related to the heart defect. It occurred in a child

Table 3 *Closure of ventricular septal defect in infancy — surgical approach*

Surgical approach	*No.*
Right atriotomy	27
Right ventriculotomy	14
Left ventriculotomy	2
Total	41*

*2 patients required 2 incisions (left ventriculotomy and right atriotomy) for closure of multiple defects.

Table 4 *Closure of ventricular septal defect in infancy — postoperative complications*

Postoperative complications	*No.*
Supraventricular tachycardia	2
Nodal rhythm	1
1st degree AV block	1
2nd degree AV block	2
3rd degree AV block	2
Convulsions	2
Residual ventricular septal defect	2
Wound infection	2

Table 5 *Closure of ventricular septal defect and debanding – surgical approach*

Surgical approach	*No.*
Right atriotomy	36
Right ventriculotomy	22
Apical left ventriculotomy	3
Total	58*

*3 patients required 2 incisions for closure of all ventricular septal defects.

with thoracic dystrophy who died from progressive chronic respiratory failure one year after operation. Apart from this late death, and the patient who has serious brain damage, all other patients are making satisfactory progress. In 4 patients there is a persistent systolic murmur without any sign of heart failure. The nature of the murmur has not yet been determined by repeat cardiac catheterisation.

(3) *Intracardiac repair and debanding of pulmonary artery*

Morbidity related to previous banding of the pulmonary artery was significant. Twenty-seven patients (46·5%) had a decreasing exercise tolerance and developed cyanosis before debanding and closure of the ventricular septal defect. All patients had cardiac catheterisation and angiocardiography before operation. Six (10·3%) had a raised pulmonary vascular resistance ($Rp/Rs \geqslant 0{\cdot}5$).

The surgical repair was performed using cardiopulmonary bypass with moderate hypothermia and intermittent cross-clamping of the aorta. The surgical approach is shown in Table 5. In 3 patients with multiple ventricular septal defects, 2 incisions were made to close all the defects. In 8 patients the defect was closed by direct suture. A prosthetic patch was used for the other patients. There were 4 hospital deaths (6·8%). The first patient was 5 years old, and the pulmonary artery had been banded at 3 months of age for a single mid-septal ventricular septal defect. The band had migrated beyond the bifurcation of the pulmonary artery. The origin of the right pulmonary artery was completely occluded and the left pulmonary artery was hypoplastic. A satisfactory reconstruction of the pulmonary arteries was not achieved at the time of operation and the patient died 8 days after operation. The necropsy confirmed that the right pulmonary artery remained occluded and histological examination showed pulmonary vascular changes in the left lung, compatible with a moderate degree of pulmonary vascular disease. The second patient had a single high ventricular septal defect and a left superior vena cava draining into the coronary sinus. Banding had been performed at 5 months of age, and the ventricular septal defect was closed and the pulmonary artery debanded at the age of 3 years. An unroofed coronary sinus (left superior vena cava draining to the coronary sinus and the left atrium) was not recognised and she became severely hypoxic after operation. At reoperation the following day, the left superior vena caval blood was redirected to the right atrium, but the patient died 24 hours later in a low cardiac output state. The other patients who were 3 years and 6 years of age had multiple ventricular septal defects and died after operation in a low cardiac output state. The younger patient had required reconstruction of both pulmonary arteries to relieve the band which had migrated beyond the bifurcation.

Patch enlargement of the main pulmonary artery was used in 47 patients (81%). Excision of the banded segment with end-to-end anastomosis was used in 6 patients; this is at present our technique of choice. Migration of the band beyond the bifurcation required extensive reconstruction of the pulmonary arteries in 5 patients, including the use of a 'dacron' tube from the main pulmonary artery to left or right pulmonary artery in 3 patients. Infundibular resection of the right ventricle was necessary in 11 patients (18·9%), and a pulmonary valvotomy in 2 (3·4%). A gradient between the right ventricle and the pulmonary artery exceeding 20 mmHg remained in 12 patients (20·6%).

Discussion

As for most operations on the heart, the determination of the ideal time for surgical repair of ventricular septal defect depends on: (1) the operative risk in relation to age; (2) the quality of the repair; (3) the preoperative detrimental effects of the disease on the myocardium and pulmonary vasculature and their reversibility; and (4) to some extent, on the psychosocial impact of the disease and its treatment on the child and its family.

Residual abnormalities in left heart size and function have been documented after closure of ventricular septal defect in older children (Jarmakani *et al.*, 1971) and seem to be reversible if the defects are closed in younger patients (less than 2 years of age (Cordell *et al.*, 1976). The same applies for pulmonary vascular changes which are reversible if the patients are operated upon when less than 2 years of age (DuShane and Kirklin, 1973). It can be argued in the light of several series of primary closure of isolated single high ventricular septal defect in infancy (Johnson *et al.*, 1974; Barratt-Boyes *et al.*, 1976; Kirklin *et al.*, 1976; Subramanian, 1976; Rein *et al.*, 1977; Sigmann *et al.*, 1977) that, if the operative mortality and quality of surgical repair are the same in infancy as beyond infancy, all large ventricular septal defects should be closed in infancy. However, this argument takes no account of the occurrence of spontaneous closure or diminution in size of the defect. Accordingly, we still believe that elective closure of these defects should not be undertaken before the age of 1 year unless clearly indicated by: (a) the persistence of congestive heart failure and its consequences in spite of a fair trial of medical treatment or, (b) the less common rising pulmonary vascular resistance in that age group.

Blackstone and his collaborators (1976) have recently attempted to bring together all these factors into an elegant equation which sums these possibilities. Their results show that cure after successful primary repair of a single large ventricular septal defect is more likely in the younger patient with a lower preoperative pulmonary vascular resistance and pulmonary artery pressure. The authors define surgical cure as survival for 5 years, with a mean pulmonary artery pressure at that time less than 25 mmHg. Their conclusion is that the optimal age for elective repair is 18 months. Since this figure is based on a higher surgical mortality in infancy than reported here, we might, therefore, conclude that the optimal age for closure is somewhat less.

Our policy for patients with single ventricular septal defect associated with patent atrial septum (excluding atrioventricular defects) or a persistent ductus arteriosus is the same as the one outlined for isolated single ventricular septal defect. For patients with multiple ventricular septal defects the mortality is still high whatever the policy adopted (Blackstone *et al.*, 1976). Whether these patients should undergo a primary closure or banding of the pulmonary artery if they require surgical treatment during infancy remains controversial. We now would consider primary closure of these defects except for the truly multiple small defects of the 'Swiss-cheese type', for which we still prefer banding of the pulmonary artery in infancy and an intracardiac repair at about 2 years of age.

When ventricular septal defect is complicated by coarctation of the aorta, our present policy is to resect the coarctation at the preliminary operation without banding the pulmonary artery, unless the infant is critically ill and deteriorates during resection of the coarctation. In this case, pulmonary artery banding would also be performed.

The difference in the mortality rate between the one-stage and two-stage approaches is considerable. The risk of pulmonary artery banding was less (12%) in this series than in previous years (Stark *et al.*, 1969). More recent reports from other institutions show a hospital mortality of 10 to 20 per cent (Patel *et al.*, 1973; Dooley *et al.*, 1975). If one assumes that the risk of debanding and closure of ventricular septal defect would be the same in our group 1 patients who survived pulmonary artery banding as in the group 3 patients, one could expect an overall mortality rate with the two-stage approach of 19·3 per cent. This is considerably higher than the operative risk of early primary closure, which was 2·4 per cent in the present series.

This consideration does not take into account the late morbidity and late mortality which remains to be assessed. Our experience so far does not suggest that late complications are more common in patients who had early correction. In addition, pulmonary artery banding may not be effective, as shown by our experience with 7 infants who survived but remained in congestive heart failure. The failure of pulmonary artery banding probably results from the difficulty in evaluating the haemodynamic effect of the band at the time of operation (Utley, 1973) and from changes in pulmonary vascular resistance after banding. If we add the patient in whom increased pulmonary vascular resistance was present at the time of intracardiac repair ($Rp/Rs > 0{\cdot}5$) to the infants with congestive heart failure after pulmonary artery banding, the failure rate was 43·6 per cent.

Our groups 1 and 2 are not entirely comparable: infants who develop intractable cardiac failure during the first 3 months of age often have more complex anomalies than those with isolated ventricular septal defect(s) and therefore are at high risk. However, if after treatment of the associated lesion(s) they remain in severe congestive heart failure related to the presence of ventricular septal defect(s), we believe our results justify a policy of primary closure rather than banding of the pulmonary artery, and that the age or weight of the patient should not contraindicate or increase the risk of primary closure.

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Echocardiographic and exercise evaluation of results of mitral valvotomy operations

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SUMMARY M-mode echocardiography was performed in 54 patients 1 month to 3 years after mitral valvotomy for dominant mitral stenosis. The mitral valve closure index (MVCI), an index previously shown to correlate well with the calculated mitral valve area, was used to diagnose residual mitral stenosis. Using the equation MVCI = 33 MVC − 12, 12 patients (22%) were deemed to have mild, 4 (7%) moderate, and 2 (4%) severe residual stenosis. Repeat cardiac catheterisation confirmed the diagnosis in 7 patients. The postoperative mitral valve closure index correlated significantly with patients' subjective symptoms and objective exercise indices. It was higher in patients in whom the posterior mitral leaflet movement became normal after valvotomy, and was lower in patients with anterior mitral leaflet excursions below 14 mm before operation. The mitral valve closure index is a sensitive index for diagnosing residual mitral stenosis after valvotomy.

Residual mitral stenosis accounts for most of the poor results after mitral valvotomy (Baker and Hancock, 1960; Higgs *et al.*, 1970). Clinical diagnosis of residual mitral stenosis is difficult without haemodynamic studies (Selzer and Cohn, 1972). Non-invasive evaluation by echocardiography would be an advantage if the technique could be shown to be reliable. Classical features such as a reduced diastolic closure rate and anterior movement of the posterior mitral leaflet are not sufficiently sensitive to enable diagnosis of lesser degrees of residual mitral stenosis to be made (Cope *et al.*, 1975; Ticzon *et al.*, 1975). We recently reported a new echocardiographic index of mitral valve closure that correlates well with the haemodynamically determined mitral valve area in patients with dominant mitral stenosis (Shiu, 1977). Valvotomy causes an increase in the mitral valve closure index in some, but not all patients. This suggests to us that the postoperative mitral valve closure index may be a simple method for the non-invasive evaluation of residual mitral stenosis. We report here a follow-up echocardiographic study of 54 patients undergoing mitral valvotomy. Echocardiographic analyses included the mitral valve closure index and the pattern of posterior mitral leaflet movement. These features were compared with patients' subjective symptoms, objective exercise indices, and, in 7 patients, postoperative haemodynamic studies.

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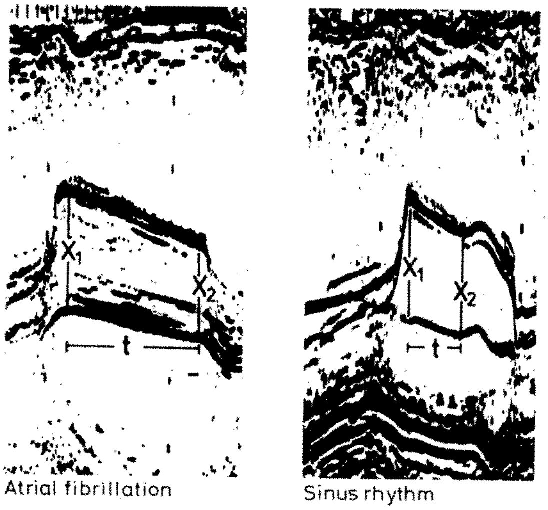
Patients and methods

The study comprised 54 patients, 10 men and 44 women aged from 15 to 64 years, operated on for lone mitral stenosis. Ten patients were in sinus rhythm and the remainder in atrial fibrillation at the time of operation: one patient developed atrial fibrillation after operation. No patient had more than grade 1/4 mitral regurgitation, tricuspid valve disease, or aortic valve disease at the time of preoperative investigation. Ten patients had open valvotomy and 44 patients closed operations using a Tubbs dilator. Ten patients had previously undergone valvotomy.

Postoperative echocardiograms were obtained from one month after operation. Most patients had repeat examinations at yearly intervals, with the longest follow-up period of 3 years. A Smith-Kline Ekoline 20 ultrasonoscope with a 2·25 MHz focused transducer was used and records were made on photographic paper at paper speeds of 50 and 100 mm/s. The mitral echogram was recorded at a level where both anterior and posterior mitral leaflets were continuously visible and where diastolic leaflet separation was maximal. Classification of anterior and posterior movement of the posterior mitral leaflet in early diastole was as defined by Duchak *et al.* (1972); in particular, biphasic opening with a net anterior movement was classified as anterior (Popp, 1976).



Atrial fibrillation Sinus rhythm

Fig. 1 *Mitral echograms from a patient in atrial fibrillation and in sinus rhythm, showing the measurements of early and late diastolic separations* (X_1 *and* X_2) *of the anterior and posterior mitral leaflets. Mitral valve closure index* (*MVCI*) $= \frac{X_1 - X_2}{X_1 \times t} \times 100$ *where t is time in seconds.*

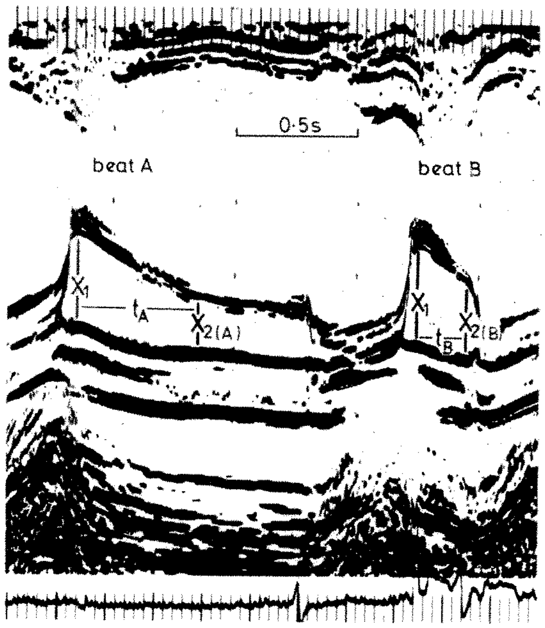


Fig. 2 *Measurement of mitral valve closure index* (*MVCI*) *in beats of long diastolic intervals. In beat A diastolic approximation of the anterior and posterior mitral leaflets has ceased before end-diastole, at* X_2 (*A*). *The mitral valve closure index* (*MVCI*) *calculated as* $\frac{X_1 - X_2}{X_1 \times tA}$ (*A*) *is similar to that of* $\frac{X_1 - X_2}{X_1 \times tB}$ (*B*).

The mitral valve closure index (MVCI) was calculated using the equation MVCI $= \frac{X_1 - X_2}{X_1 \times t} \times 100$ per cent where X_1 and X_2 are the early and late diastolic separations of the anterior and posterior mitral leaflet echoes, and 't' the time in seconds between the two measurements (Fig. 1). Mitral echograms not showing both mitral leaflets throughout diastole were rejected, as were those with diastolic intervals shorter than 200 ms. Where leaflet closure stopped before end-diastole, such as during long diastolic intervals, X_2 was measured at the time leaflet closure ceased (Fig. 2).

Symptomatic grading (New York Heart Association Classification) and exercise testing were done at least 3 months after operation. Measurements of mitral valve closure index nearest to the third postoperative month were taken for comparison with symptoms and exercise tests.

Exercise tests were performed on a bicycle ergometer using a standard multistaged regimen. Thirty-three patients were exercised to a satisfactory end point of either dyspnoea or fatigue. Maximum exercise capacity was defined as the highest work load (in kilopond metres per min) sustained for 2 minutes. Patients were then rested and 19 patients performed submaximal exercise for 4 minutes with collection of expired air during the last minute. On and off line gas analysis using a Mass Spectrometer (20th Century Electronics Ltd.) and an electronic spirometer (Mercury Electronics Ltd. ĊS6) allowed estimation of oxygen uptake and cardiac output during submaximal exercise. The exercise tests were conducted by one of us (A.C.) with no knowledge of the patients' symptomatic grading or echocardiographic results.

REPEAT HAEMODYNAMIC STUDIES

Postoperative cardiac catheterisation was performed in 7 patients 1 to 3 years after valvotomy. The reason for repeat study was persistent symptoms of dyspnoea in 6 patients, and recent onset angina in the seventh. All patients had left and right heart catheterisation including direct left atrial pressure measurements by transseptal pucture. Mitral valve areas were calculated from the mean diastolic mitral gradient using direct left atrial and left ventricular pressures, and cardiac output using duplicate dye dilution curves (Gorlin and Gorlin, 1951).

Results

POSTOPERATIVE MITRAL VALVE CLOSURE INDEX

The postoperative mitral valve closure index (MVCI) in the 54 patients studied ranged from 0 to 180 (90 ± 6), and was below 70 in 18 patients. Using the regression equation MVCI = 33 × MVA − 12 (Shiu, 1977), these 18 patients were deemed to have residual mitral stenosis with estimated mitral valve areas below 2·5 cm². These patients were further subdivided according to their postoperative mitral valve closure index, using the ranges 0 to 30, 31 to 50, 51 to 70 to represent the respective mitral valve areas of < 1·3 cm², 1·3 to 1·7 cm², and 1·8 to 2·5 cm². By this method, 12 (22%) patients had mild, 4 (7%) moderate, and 2 (4%) severe residual stenosis (Fig. 3).

FUNCTIONAL CLASS

The distribution of the postoperative mitral valve closure indices according to functional class is shown in Fig. 4. Twenty-one patients were asymptomatic (Class 1) and their mean mitral valve closure index (110 ± 6) was significantly higher than patients with residual symptoms (P < 0·005). Twenty-five patients were in functional class II and 6 were in class III (mean closure index 75 ± 6 and 50 ± 11, respectively). Two patients left the country before evaluation at 3 months and were not included.

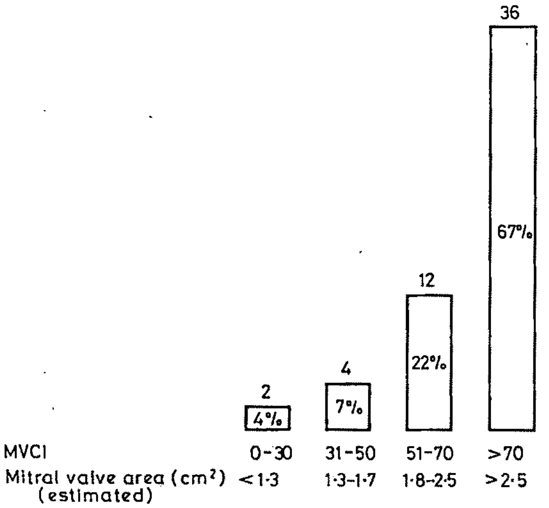


Fig. 3 *Incidence of various degrees of residual mitral stenosis as shown by the distribution of the postoperative mitral valve closure index (MVCI) in 54 patients. The mitral valve areas were estimated using the regression equation MVCI = 33, MVA = 12 (Shiu, 1977).*

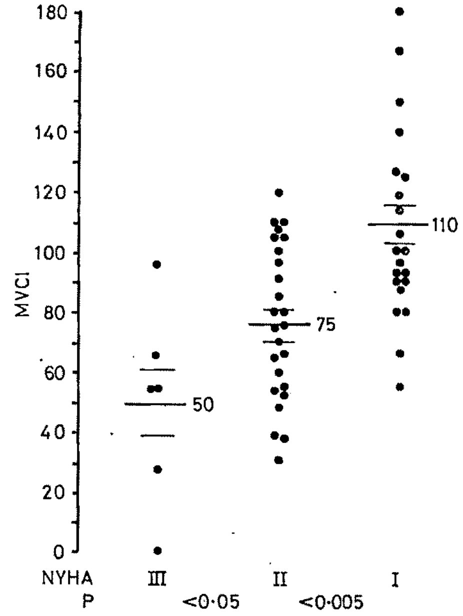


Fig. 4 *Distribution of postoperative mitral valve closure index (MVCI) in 52 patients according to postoperative symptoms. Though the mean MVCIs are significantly different for each group, considerable overlap between the groups reflects the poor correlation between symptoms and residual mitral stenosis.*

EXERCISE INDICES

Patients with low postoperative mitral valve closure indices performed worse in the exercise tests. Maximum work-load correlated significantly with the postoperative mitral valve closure index in both

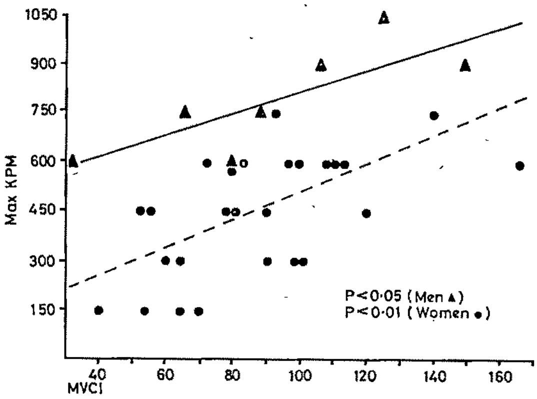


Fig. 5 *Correlation between maximum exercise capacity (in kilopond metres/min) and postoperative mitral valve closure index (MVCI) in 33 patients. As expected, male patients had higher exercise capacities than female patients given the same MVCI.*

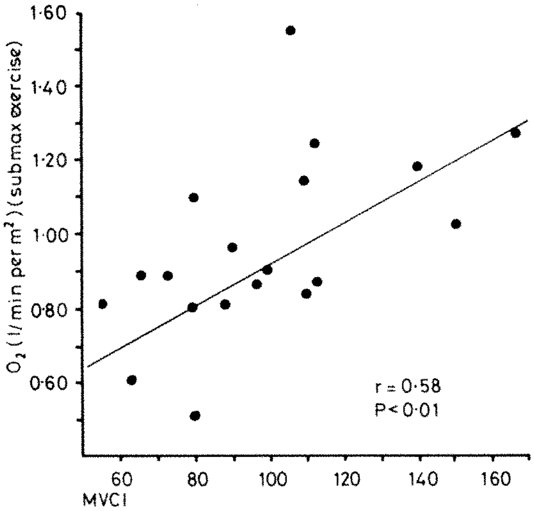


Fig. 6 *Correlation between oxygen uptake during submaximal exercise and postoperative mitral valve closure index (MVCI) in 19 patients.*

men and women ($P < 0.05$ for men; $P < 0.01$ for women; Fig. 5). As might be expected, in patients with comparable mitral valve closure indices, male patients achieved higher maximum work loads than female patients.

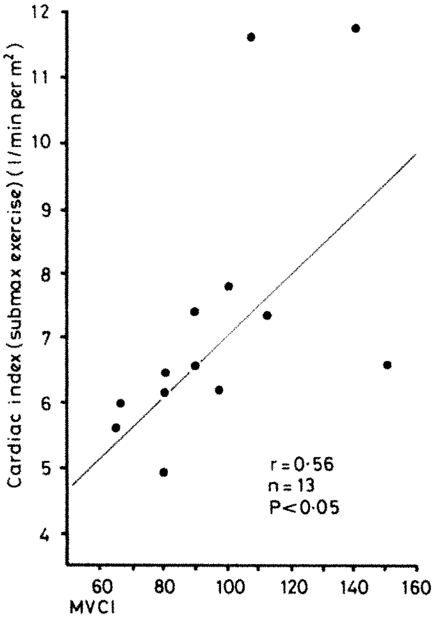


Fig. 7 *Correlation between cardiac index during submaximal exercise and postoperative mitral valve closure index (MVCI) in 13 patients.*

Difficulties with expired air collection during submaximal exercise reduced the number of patients to 19 for oxygen uptake and 13 for cardiac index measurements. Again, patients with higher postoperative levels achieved significantly higher oxygen uptake and cardiac indices during submaximal exercise ($P < 0.01$ and $P < 0.05$, respectively. Fig. 6 and 7).

REPEAT HAEMODYNAMIC STUDIES

Fig. 8 shows the haemodynamic and echocardiographic findings in the 7 patients who had repeat cardiac catheterisation after valvotomy. In the 2 patients with a postoperative mitral valve closure index lower than 30 severe stenosis was confirmed. One of them subsequently had a mitral valve replacement; the other was considered too high a risk on other grounds for further operation. Two patients with mitral valve closure indices over 90 had no residual stenosis. Though the number was small, the correlation between mitral valve closure index and mitral valve area appeared unchanged after valvotomy.

POSTERIOR MITRAL LEAFLET MOVEMENT BEFORE AND AFTER VALVOTOMY

Analysis of echocardiographic posterior mitral leaflet movement before valvotomy in 45 patients showed anterior movement in 38 (84%) and posterior movement in 7 (16%). Abnormal anterior movement remained after valvotomy in 18 patients, and the movement became posterior in 20 (Fig. 9).

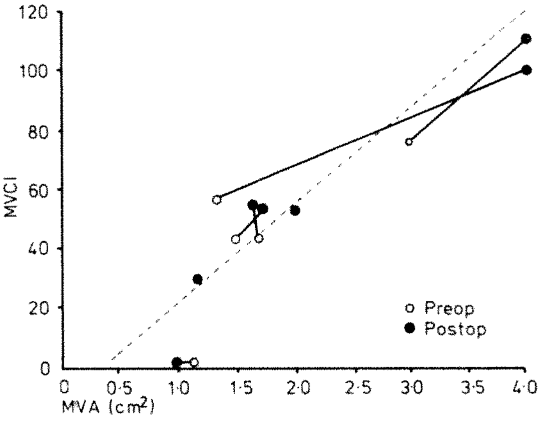


Fig. 8 *Correlation between mitral valve closure index (MVCI) and calculated mitral valve area from haemodynamic data in 7 patients investigated after valvotomy operations (black dots). Five of the 7 patients also had preoperative measurements of both (circles). The dotted line is the regression line between MVCI and mitral valve area in 40 patients before valvotomy.*

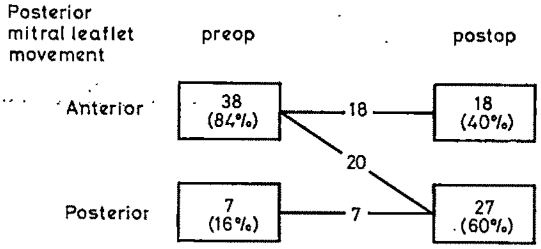


Fig. 9 *Early diastolic movement of the posterior mitral leaflet in 45 patients before and after valvotomy. Of the 38 patients with anterior posterior mitral leaflet movement before surgery, 18 showed no change and 20 showed normal posterior movement afterwards.*

Patients with posterior mitral leaflet movement before valvotomy showed no change.

In Fig. 10, 42 of these patients were divided into 3 groups according to their posterior mitral leaflet movement before and after valvotomy. The postoperative mitral valve closure index was highest in the group in whom posterior mitral leaflet movement was anterior before operation but posterior afterwards (108 ± 7, $P < 0{\cdot}001$). The lowest postoperative mitral valve closure indices were found in those patients whose posterior mitral leaflet remained anterior after operation (73 ± 8). Though patients with normal posterior mitral leaflet movement had the highest preoperative mitral valve closure index (40 ± 10), their postoperative mitral valve closure indices (77 ± 11) were not significantly higher than those patients who had persistently anterior posterior mitral leaflet movement after operation.

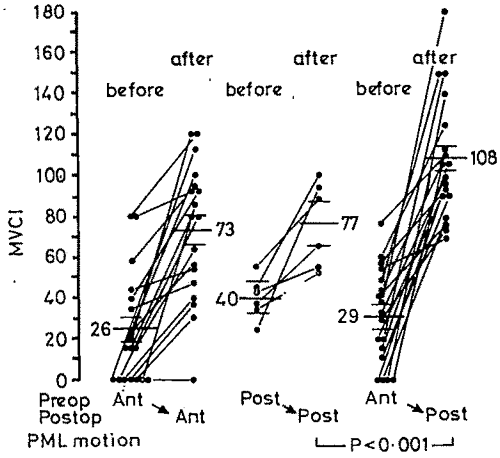


Fig. 10 *Pre- and postoperative mitral valve closure index (MVCI) in 43 patients grouped according to posterior mitral leaflet motion before and after valvotomy. The change in mean mitral valve closure index (MVCI) (shown with SEM) for each group is shown. Patients in whom posterior mitral (PML) movement became normal as a result of the operation had significantly higher postoperative MVCI than the rest. Patients in whom PML movement was posterior before operation had the smallest increase in mean MVCI.*

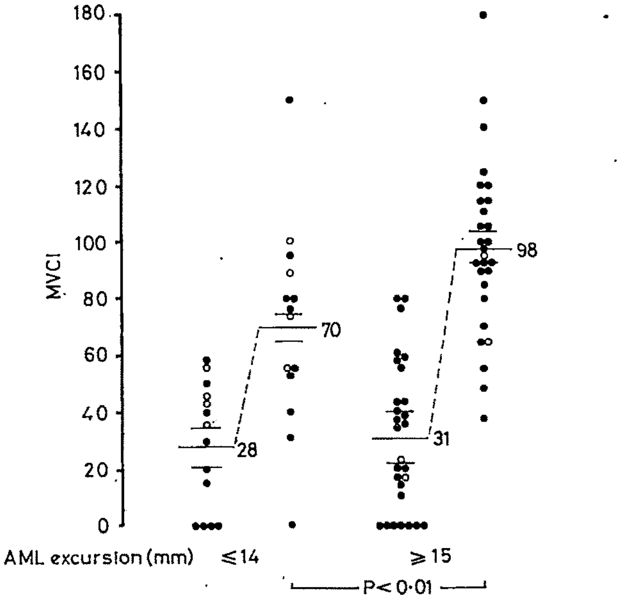


Fig. 11 *Pre- and postoperative mitral valve closure index (MVCI) in 42 patients grouped according to whether anterior mitral leaflet (AML) excursion was greater or less than 14 mm. Mean and SEM are shown. Despite similar preoperative MVCI, patients with lower postoperative anterior mitral leaflet (AML) excursions had significantly lower MVCI. Open circles represent patients who also had normal posterior mitral leaflet movement before valvotomy.*

PREOPERATIVE ANTERIOR MITRAL LEAFLET EXCURSION

In the 42 patients for whom preoperative echocardiograms were available, 14 had anterior mitral leaflet excursions below 14 mm and their postoperative mitral valve closure indices were significantly lower than the rest (70 ± 7 and 98 ± 6, respectively, $P < 0{\cdot}01$, Fig. 11). Four patients with abnormally low excursions also had posterior diastolic movement of the posterior mitral leaflet.

Discussion

Lasting haemodynamic and symptomatic improvement after mitral valvotomy depends on adequate

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relief of the mitral obstruction (Ellis *et al.*, 1959; Baker and Hancock, 1960). The true incidence of residual stenosis after mitral valvotomy may be higher than suspected on clinical grounds (Selzer and Cohn, 1972). Feigenbaum *et al.* (1968) and Higgs *et al.* (1970) showed that persistence of symptoms or their return after a period of apparent improvement was most often the result of residual stenosis and not mitral regurgitation or restenosis. In Feigenbaum *et al.*'s (1968) study, pre- and postoperative investigations showed that the change in the mitral valve area varied from $-0{\cdot}1$ cm^2 to $+3{\cdot}8$ cm^2. Similarly, Mullin *et al.* (1972) found that the postoperative mitral valve area in 12 patients ranged from 1·4 cm^2 to 3·6 cm^2.

Routine echocardiographic examination of patients after mitral valvotomy would disclose more patients with residual mitral stenosis than suspected clinically. The classical echocardiographic criteria for mitral stenosis are a slow diastolic closure rate and anterior movement of the posterior mitral leaflet. Neither of these features is sufficiently sensitive to allow confident diagnosis of residual stenosis. The diastolic closure rate has been shown to increase after valvotomy (Edler, 1967) but more recent studies showed that this measurement correlated poorly with valve area as determined haemodynamically (Cope *et al.*, 1975; Nichol *et al.*, 1977; Shiu, 1977). 'Normal' posterior movement of the posterior mitral leaflet has been reported in up to 17 per cent of patients with true and sometimes severe mitral stenosis so that posterior mitral leaflet movement alone cannot be relied on to diagnose residual stenosis.

The rationale behind the measurement of mitral valve closure index is that mitral valve closure is delayed in mitral stenosis proportionate to the severity of the obstruction. The fundamental difference between the mitral valve closure index

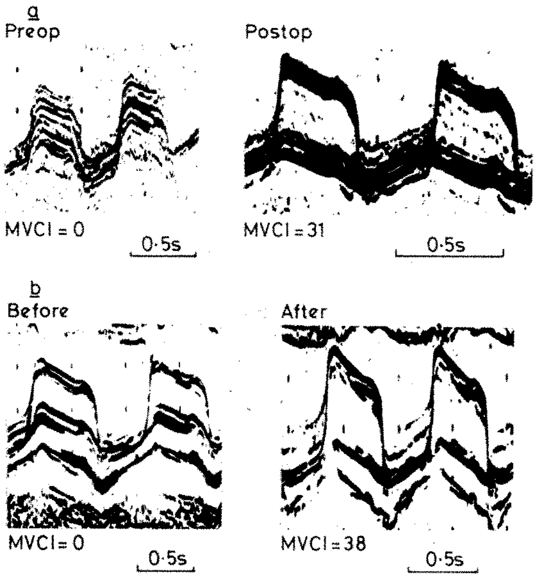


Fig. 12 *Pre- and postoperative mitral echograms in 2 patients in whom posterior mitral leaflet movement remained anterior after valvotomy. The postoperative mitral valve closure index (MVCI) of both patients is in the moderate to severe stenosis range.*

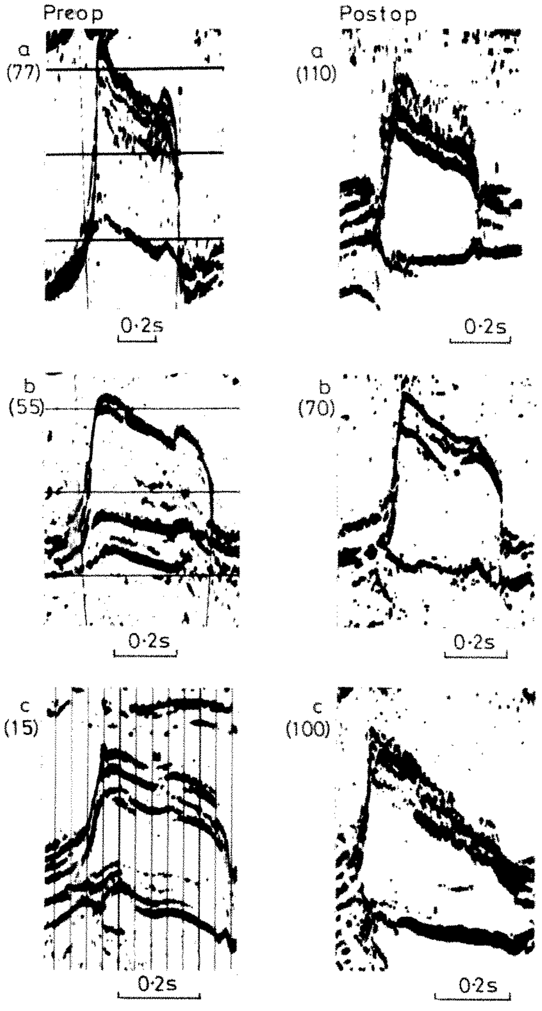


Fig. 13 *Pre- and postoperative mitral echograms in 3 patients in whom posterior mitral leaflet movement became normal after valvotomy. Numbers in brackets are the mitral valve closure index (MVCI). No patient showing such a change had a postoperative MVCI below 70.*

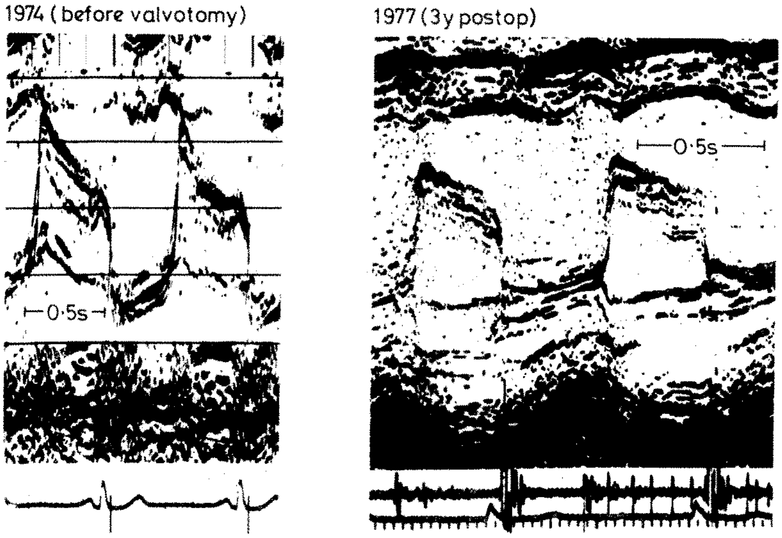
and the diastolic closure rate is that the mitral valve closure index measures the intrinsic rate of closure of the two mitral leaflets while the diastolic closure rate measures anterior mitral leaflet movement plus mitral ring and other movements not relevant to valve closure. The relation between mitral valve closure index and haemodynamically determined mitral valve area found in preoperative patients would be expected to remain after mitral valvotomy, since residual mitral stenosis will again cause delayed valve closure.

We have chosen an arbitrary postoperative mitral valve closure index of 70 below which we consider that residual stenosis is present. From the previous study in preoperative patients, this value is equivalent to a mitral valve area of 2·5 cm^2. By this criterion, one-third of our patients have residual stenosis. Of these 18 patients, 12 had mild, 4 moderate, and 2 severe stenosis as judged from their mitral valve closure index. Seven patients—5 with residual mitral stenosis and 2 without—had haemodynamically determined mitral valve areas in close agreement with that estimated by their mitral valve closure index.

The postoperative mitral valve closure indices were significantly different in patients of different functional classes (Fig. 4). Even more importantly, patients with higher postoperative mitral valve closure index achieved higher maximum exercise levels and had higher oxygen uptake and cardiac indices during submaximal exercise. While factors such as patient co-operation, left ventricular function, and mitral regurgitation may influence results of exercise tests, it is likely that residual mitral stenosis is the major limiting factor in these patients. Certainly Feigenbaum *et al.* (1968) showed that increases in cardiac index and falls in pulmonary vascular resistance correlated closely with increases in valve areas.

A change from anterior to posterior movement of the posterior mitral leaflet has been taken to indicate a successful valvotomy (Feigenbaum, 1976). In this study, those patients in whom the posterior mitral leaflet remained anterior after valvotomy had a significantly lower postoperative mitral valve closure index than those in whom posterior mitral leaflet movement became normal (Fig. 11, 12, and 13). Residual stenosis, as defined by a postoperative mitral valve closure index of below 70, was not seen in any of the patients in whom posterior mitral leaflet movement became normal, but was found in 50 per cent of patients in whom anterior posterior mitral leaflet persisted.

Two features in the preoperative echocardiogram were found to be associated with an increased incidence of residual mitral stenosis. These are an anterior mitral leaflet excursion of below 14 mm, and posterior diastolic movement of the posterior mitral leaflet. Low anterior mitral leaflet excursion has been known to be a relative contraindication for mitral valvotomy (Nanda *et al.*, 1975). The other finding was less expected, but supports the concept that normal posterior mitral leaflet movement, despite the presence of significant mitral stenosis,


1974 (before valvotomy)

1977 (3y postop)

Fig. 14 *Pre- and postoperative echocardiograms in a patient followed up for 3 years. Normal posterior mitral leaflet movement persisted from the time of valvotomy.*

denotes cuspal rather than commissural disease (Ticzon *et al.*, 1975; Shiu *et al.*, 1978), and thus will not be improved by mitral valvotomy.

None of our patients showed a significant reduction in the mitral valve closure index or change in posterior mitral leaflet movement on repeated examination after valvotomy (Fig. 14). Longitudinal studies over a longer period may show such changes and throw light on the incidence of mitral restenosis and on whether restenosis is commonly the result of commissural refusion or progressive cuspal disease.

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Assessment of left-to-right shunt and left ventricular function in isolated ventricular septal defect

Echocardiographic study

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SUMMARY This echocardiographic study was designed to assess left ventricular function and pulmonary blood flow in ventricular septal defect. Fifty-one patients aged 2 weeks to 21 years were investigated (group 2). Five of 10 operated patients were studied one week after surgical closure of the defect (group 3) and seven 3 to 6 weeks postoperatively (group 4). The control group consisted of 45 normal subjects aged 2 weeks to 21 years (group 1).

Left atrium/aortic root dimension ratio (LA/Ao) was used to express the pulmonary systemic flow ratio. Left ventricular chamber size was assessed by measurement of left ventricular end-diastolic dimension and volume. The left ventricular mass and the ratio of end-diastolic volume to left ventricular mass were determined to relate the degree of left ventricular hypertrophy to volume overload. Myocardial function was evaluated using ejection phase indices. Ventricular septal thickness, posterior wall thickness, and echocardiographic patterns of septal motion were also studied.

The left atrium/aortic root dimension, end-diastolic volume, and left ventricular mass were significantly greater in group 2 patients ($P < 0{\cdot}05$) than in the normal controls. There was a very good correlation between LA/Ao and pulmonary/systemic flow ratio ($r = 0{\cdot}83$). Eleven of the group 2 patients showed asymmetric septal hypertrophy (unrelated to shunt size) but left ventricular function as assessed by ejection phase indices appeared unimpaired. Immediately after operation (group 3) there was a deterioration in left ventricular function in 5 patients as shown by reduced ejection fraction, mean velocity of circumferential shortening, and relative changes in minor axis with systole. Septal motion was impaired but returned to normal in 3 to 6 weeks in 7 patients (group 4). Left atrial/aortic root dimension, end-diastolic volume, and left ventricular mass decreased significantly immediately after operation (group 3) but were still raised at 3 to 6 weeks (group 4).

Echocardiography has been shown to be a useful diagnostic tool in estimation of left-to-right shunts and assessment of serial changes in shunt size (Carter and Bowman, 1973; Silverman *et al.*, 1974; Lewis and Takahashi, 1976). Various indices of left ventricular function can now be evaluated by this technique. Left heart volumes, ejection phase indices, and left ventricular mass can be assessed reliably and have shown good correlation with data obtained at angiocardiography (Pombo *et al.*, 1971; Fortuin *et al.*, 1972; Troy *et al.*, 1972; Kaye *et al.*, 1974; Meyer *et al.*, 1975; Bennett and Rowlands, 1976). Since no single measurement is always a reliable index of contractility in the intact circulation, we have examined the usefulness of several indices for detecting functional abnormality of the left ventricle in ventricular septal defect.

Recognition of echocardiographic patterns of interventricular septal motion is important because reversed or intermediate septal motion precludes accurate assessment of left ventricular function. A useful method of assessing the appropriateness of myocardial hypertrophy would be to relate left ventricular mass to end-diastolic volume (EDV); we have, therefore, determined the ratio of EDV/left ventricular mass to assess hypertrophy. This index has been used previously (Jarmakani *et al.*, 1972) for evaluating left ventricular contractile state

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in patients with chronic volume overload caused by large left-to-right shunts.

The present study was designed to provide information about the size of left-to-right shunt, left ventricular chamber dimension, left ventricular mass, and myocardial function in patients with ventricular septal defect. We have used echocardiographic indices that are easily obtained, useful, and repeatable on an out-patient basis without any discomfort or risk to the child or inconvenience to the parents.

Subjects and methods

Patients were classified as follows: Group 1 consisted of 45 normal control subjects matched for age and sex and without clinical evidence of cardiovascular disease. Group 2 consisted of 51 patients with ventricular septal defect. Their ages ranged from 2 weeks to 21 years, mean 6·2 years; 23 were male and 28 female.

Cardiac catheterisation was carried out in 35 patients. Twenty-three had large shunts ($\dot{Q}p:\dot{Q}s \geqslant 2:1$), 8 with normal pulmonary artery pressure (PAP/SAP ratio $< 0·40$) and 15 with pulmonary arterial hypertension. There were 6 patients with a small residual postoperative ventricular septal defect. There were 6 patients with small unoperated defects.

A summary of the haemodynamic data is given in Table 1.

Surgical closure of the defects was performed in 10, through a right atriotomy via the tricuspid valve in one and through a right ventriculotomy in the remainder.

Group 3 consisted of 5 patients on whom an echocardiographic examination was performed 1 week after surgical repair of ventricular septal defect. Group 4 consisted of 7 patients on whom studies were repeated at 3 to 6 weeks after operation.

Left ventricular, aortic root, and left atrial echocardiograms were recorded by the standard methods (Feigenbaum, 1972) with a Smith-Kline Ekoline ultrasonoscope using a 2·5 MHz focused transducer with a repetition cycle of 1000 impulses/s, connected to a Cambridge Strip chart recorder. Simultaneous electrocardiograms were also re-

Table 1 *Haemodynamic data in patients with ventricular septal defect*

Case no.	*Age*	*BSA* *(m^2)*	*$\dot{Q}p:\dot{Q}s$*	*PAP/SAP ratio*	*Rp:Rs*
1	2 wk	0·20	1·7	0·53	0·17
2	3 wk	0·24	2·4	0·37	0·15
3	5 m	0·27	3·5	0·66	0·20
4	6 m	0·27	2·2	0·44	0·18
5	6 m	0·30	2·6	0·93	0·48
7	1 y 1 m	0·50	2·5	0·45	0·20
8	1 y 1 m	0·41	2·1	0·28	0·19
9	1 y 5 m	0·45	2·9	1·00	0·34
10	1 y 5 m	0·50	2·8	0·46	0·16
12	1 y 5 m	0·40	3·1	0·78	0·16
14	1 y 11 m	0·41	3·2	0·78	0·44
15	2 y 2 m	0·54	2·1	1·02	0·36
17	3 y	0·62	1·6	0·54	0·20
18	3 y	0·52	2·0	0·33	0·18
19	3½ y	0·63	1·6	0·36	0·34
20	3½ y	0·61	2·2	0·27	0·15
22	4 y	0·67	3·0	0·75	0·20
26	5 y	0·68	1·0	0·36	0·34
27	5 y	0·68	1·0	0·30	0·18
29	6 y	0·72	1·6	0·25	0·15
30	6 y	0·68	1·5	0·26	0·24
32	7 y	0·80	2·0	0·97	0·43
33	7 y	0·74	1·2	0·12	0·11
34	7½ y	0·87	3·0	0·20	0·18
36	7½ y	0·78	2·1	0·17	0·16
38	9 y	0·89	2·8	0·83	0·10
39	9½ y	0·94	2·0	0·15	0·15
41	10½ y	1·40	1·5	0·31	0·15
42	11 y	1·29	1·0	0·20	0·18
43	11 y	1·20	1·5	0·40	0·15
44	11 y	1·25	3·2	0·56	0·19
46	13 y	1·28	2·5	0·60	0·20
48	15 y	1·34	1·4	0·38	0·25
49	16 y	1·26	2·2	0·60	0·27
50	20 y	1·65	2·0	0·29	0·12

Abbreviations: BSA = body surface area, $\dot{Q}p:\dot{Q}s$ = pulmonary/systemic flow ratio, PAP/SAP ratio = pulmonary artery/systemic artery pressure ratio, Rp:Rs = pulmonary/systemic resistance ratio.

corded. Left ventricular echocardiograms showing clear simultaneous echoes from the endocardium of the posterior wall and the left side of interventricular septum were selected for this study. Clear identification of at least one aortic valve cusp was required for measuring aortic root dimension.

ECHOCARDIOGRAPHIC CALCULATIONS

Left ventricular dimension at end-diastole (Dd) and end-systole (Ds), left ventricular ejection time (LVET), interventricular septal thickness (IVS), left ventricular posterior wall thickness at end-diastole (PWd) and end-systole (PWs), and posterior wall excursion (PWE) were measured as illustrated in Fig. 1. Left atrial dimension (LA) was measured from the anterior edge of the posterior aortic wall to the anterior edge of the posterior left atrial wall at the end of T wave. The aortic root dimension (Ao) was measured from the anterior edge of anterior aortic wall to the anterior edge of posterior aortic wall at the peak of R wave of the electrocardiogram which was recorded simultaneously (Fig. 2). LA/Ao root dimension ratio was derived from average values for LA and Ao dimension in each case. Estimates of left ventricular end-diastolic volume (EDV) and mass were calculated by methods previously described (Rackley *et al.*, 1964; Dodge and Baxley, 1969; Troy *et al.*, 1972; Bennett and Rowlands, 1976), from the echocardiographic ventricular dimensions and posterior wall thickness by the volume formula of a prolate ellipse. All the measurements of volume and mass were corrected for body surface area (BSA) to facilitate comparison of patients of different age and size. Stroke volume (SV) was calculated by subtracting end-systolic volume (ESV) from EDV, and ejection fraction (EF) was $\frac{\text{SV}}{\text{EDV}}$. The relative change in minor axis with systole (%Δs) was expressed as $\frac{\text{Dd-Ds}}{\text{Dd}} \times 100$ per cent. Mean normalised systolic ejection rate (MNSER) was calculated as $\frac{\text{EDV-ESV}}{\text{LVET} \times \text{EDV}}$(end-diastolic volumes/s). Mean velocity of circumferential fibre shortening (Vcf) was obtained using the formula $\frac{\text{Dd-Ds}}{\text{LVET} \times \text{Dd}}$ (circ/s) while mean normalised posterior wall velocity (Vpw) was determined from the equation: $\text{Vpw} = \frac{\text{PWE}}{\text{LVET} \times \text{Dd}}$ (s^{-1}) (Quinones *et al.*, 1974). All the echocardio-

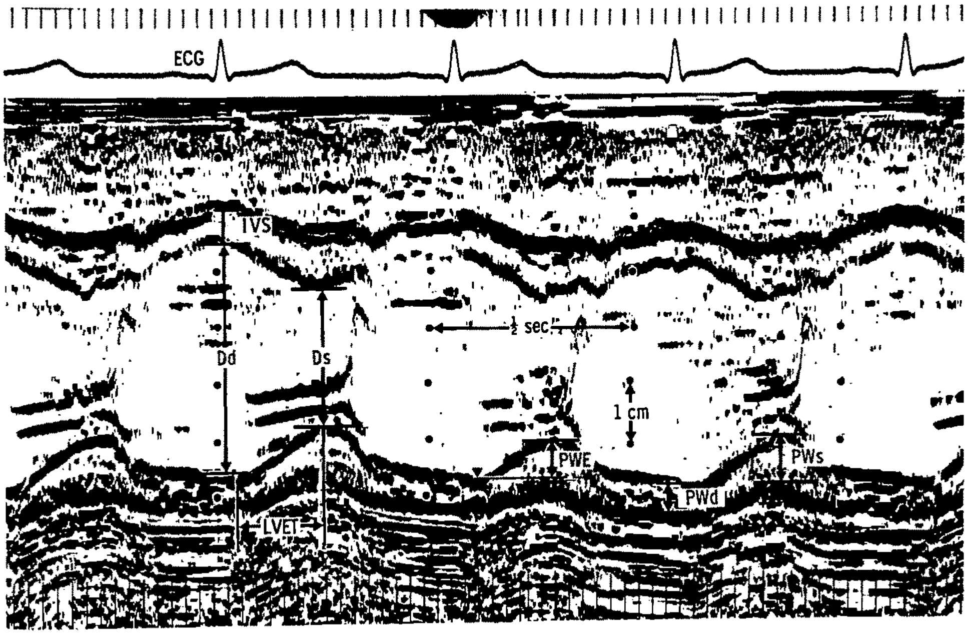


Fig. 1 *Left ventricular echocardiogram from a patient with ventricular septal defect, to illustrate measurement of end-diastolic and end-systolic dimensions (Dd and Ds), interventricular septal thickness (IVS), posterior wall thickness at end-diastole and end-systole (PWd and PWs), posterior wall excursion (PWE), and ejection time (LVET).*

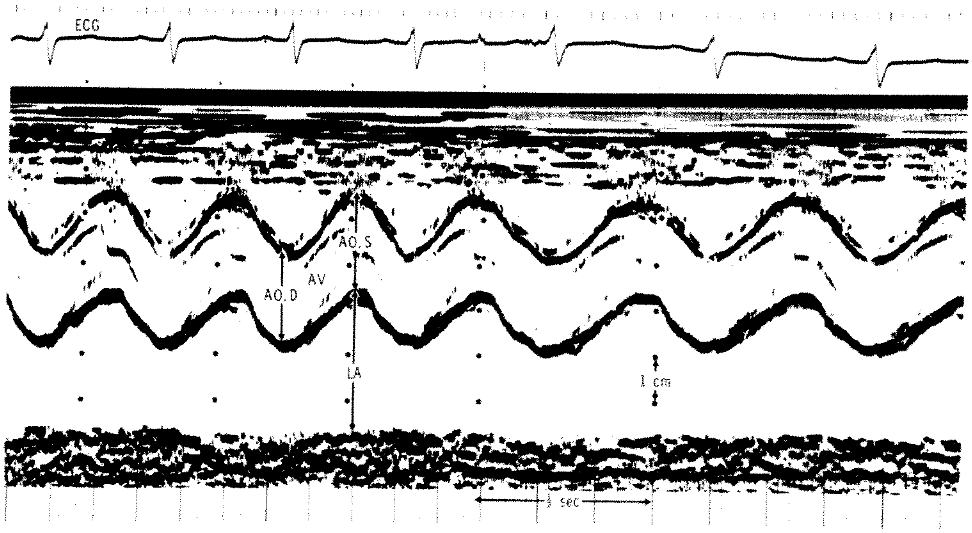


Fig. 2 *Aortic root and left atrial (LA) echocardiogram from a patient with ventricular septal defect, to illustrate measurement of left atrial dimension and aortic root dimension at end-diastole and end-systole (Ao D and Ao S).*

graphic measurements were made without knowledge of the haemodynamic state of the patients. Each dimension was measured over 3 consecutive cardiac cycles and the measurements averaged. Data obtained from all groups were punched on IBM cards and all calculations were performed on CDC 7600 computer system. The control values obtained in group 1 subjects were compared with those from patients with ventricular septal defect using 2 samples t test. In group 2, LA/Ao ratios were also compared, by linear regression analysis, with the $\dot{Q}p:\dot{Q}s$ ratios obtained at cardiac catheterisation. Similarly, the cardiothoracic ratio on plain chest radiographs was related to echocardiographic EDV.

Results

The results are given in detail in Tables 2 to 6 and Fig. 3 and 4.

LEFT VENTRICULAR END-DIASTOLIC DIMENSION

The mean of left ventricular end-diastolic dimension (Dd) was 3·4 ± 0·8 cm (mean ± SD) in group 1 and 3·7 ± 0·9 cm in group 2, which was not significantly different. However, when Dd was corrected for body surface area, the resultant values were 4·6 ± 1·2 and 5·5 ± 1·7 cm per m^2 in groups 1 and 2, respectively, showing a definite increase in left ventricular dimension in group 2 ($P < 0·05$). After closure of the ventricular septal defect, Dd fell to normal in all patients in group 3. Though there was further reduction in this index in group 4, the difference was not statistically significant.

LEFT VENTRICULAR END-DIASTOLIC VOLUME

The mean of EDV was 51·8 ± 15·5 ml per m^2 in group 1 but was significantly greater (75 ± 30·6 ml per m^2) in group 2 ($P < 0·05$). As would be expected, EDV fell significantly after operation (group 3). There was, however, no further substantial reduction in group 4 (Table 4). Cardiothoracic ratio on plain chest radiographs correlated poorly with echocardiographic EDV (Fig. 4).

LEFT VENTRICULAR MASS

The end-diastolic estimate of left ventricular mass (44·0 ± 8·8 g per m^2) in group 1 was significantly less than in group 2 (63·6 ± 21·2 g per m^2) ($P < 0·001$). Left ventricular mass remained relatively unchanged after operation (group 3) (Table 4). Though group 4 showed a significant reduction in left ventricular mass ($P < 0·001$) it remained slightly higher than in group 1 (Table 5).

LEFT VENTRICULAR END-DIASTOLIC VOLUME/LEFT VENTRICULAR MASS RATIO

EDV/LV mass ratio in group 1 (1·16 ± 0·22) was not significantly different from group 2 (1·20 ± 0·27), suggesting that there was little left ven-

Table 2 *Echocardiographic data from normal controls (group I)*

Case no.	*Age*	*Sex*	*BSA* (m^2)	*Dd* (*cm*)	(*cm per* m^2)	*EF*	*Vcf* (*circ/s*)	*Vpw* (s^{-1})	%Δs	*MNSER* (*EDVs/s*)	*PWd* (*cm*)	*IVS* (*cm*)	*IVS/PW ratio*	*EDV* (*ml per* m^2)	*LV mass* (*g per* m^2)	*EDV/LV mass ratio*	*LA* (*cm*)	*Ao* (*cm*)	*LA/Ao ratio*
1	2 wk	M	0·24	1·7	7·0	73	1·96	1·63	35	4·07	0·3	0·3	1·0	18·7	24·6	0·76	1·0	0·9	1·11
2	3 m	F	0·30	2·2	7·1	79	1·51	1·29	32	3·43	0·3	0·4	1·3	37·0	31·9	1·15	1·4	1·3	1·07
3	5 m	F	0·32	2·3	7·1	72	2·04	1·27	34	3·93	0·3	0·3	1·0	38·6	31·8	1·21	1·7	1·5	1·13
4	6 m	F	0·30	2·1	7·0	76	1·58	1·08	38	3·21	0·4	0·5	1·2	29·3	41·0	0·71	1·6	1·4	1·14
5	8 m	M	0·42	2·5	5·9	73	2·00	1·33	36	3·97	0·4	0·4	1·0	35·9	40·0	0·89	1·6	1·4	1·14
6	1 y	M	0·37	2·3	6·2	81	1·81	0·90	43	3·44	0·3	0·3	1·0	31·3	27·5	1·13	1·7	1·6	1·06
7	1 y 1 m	M	0·50	2·6	5·2	67	1·53	1·34	31	3·03	0·4	0·5	1·2	36·8	37·6	0·97	1·8	1·6	1·12
8	1 y 4 m	M	0·46	2·7	5·8	75	1·68	1·11	37	3·47	0·4	0·5	1·2	41·5	41·9	0·99	1·9	1·7	1·11
9	1 y 5 m	F	0·50	2·8	5·6	77	1·96	1·25	39	4·02	0·4	0·5	1·2	46·0	42·8	1·07	1·7	1·6	1·06
10	1 y 6 m	F	0·52	2·8	5·4	77	1·63	0·97	39	3·35	0·3	0·3	1·0	44·2	29·2	1·51	1·9	1·7	1·11
11	2 y	M	0·55	2·8	5·1	68	1·39	0·93	32	3·13	0·4	0·5	1·2	41·8	38·9	1·07	1·9	1·8	1·05
12	2 y	F	0·58	3·0	5·2	75	1·46	1·06	36	3·09	0·4	0·4	1·0	48·8	41·9	1·16	1·9	1·7	1·11
13	2½ y	M	0·60	2·6	4·3	72	1·44	1·08	34	3·18	0·5	0·5	1·0	31·8	41·3	0·76	2·3	2·0	1·15
14	3 y	F	0·59	2·9	4·9	72	1·43	1·00	34	3·04	0·4	0·4	1·0	40·3	38·3	1·03	2·1	1·8	1·17
15	3 y	F	0·62	2·8	4·5	73	1·37	1·22	35	2·82	0·5	0·5	1·0	37·1	45·5	0·81	1·7	1·6	1·06
16	3½ y	F	0·63	2·8	4·4	74	1·78	1·26	35	3·67	0·4	0·5	1·2	36·5	38·7	0·94	2·3	2·1	1·09
17	3½ y	M	0·67	3·4	5·1	79	1·59	0·90	41	3·06	0·4	0·4	1·0	61·5	45·4	1·35	2·4	2·1	1·14
18	4 y	M	0·61	3·1	5·1	80	1·74	1·20	41	3·29	0·4	0·4	1·0	47·9	40·8	1·17	2·2	2·0	1·10
19	4 y	F	0·66	2·9	4·4	80	1·47	0·98	41	2·89	0·4	0·5	1·2	36·0	33·3	1·08	2·2	1·9	1·15
20	5 y	M	0·72	3·8	5·3	77	1·51	1·13	39	3·07	0·5	0·6	1·2	79·8	51·9	1·18	2·1	2·2	0·95
21	5 y	M	0·70	3·1	4·4	73	1·54	1·12	35	3·09	0·4	0·5	1·2	41·7	35·6	1·17	2·2	2·2	1·00
22	5 y	F	0·69	3·5	5·1	71	1·31	0·91	31	2·79	0·4	0·5	1·2	61·4	45·0	1·36	2·5	2·1	1·19
23	5½ y	M	0·72	3·8	5·3	74	1·36	0·84	36	2·76	0·4	0·4	1·0	79·8	51·8	1·54	2·5	2·2	1·13
24	6 y	M	0·75	4·0	5·3	75	1·44	0·96	37	2·97	0·4	0·5	1·2	89·3	54·8	1·62	2·6	2·2	1·18
25	6 y	M	0·71	3·4	4·8	73	1·35	0·90	35	2·80	0·4	0·4	1·0	58·0	42·8	1·35	2·5	2·1	1·19
26	7 y	F	0·73	3·3	4·5	77	1·40	1·19	39	2·72	0·4	0·5	1·2	48·0	38·2	1·26	1·9	1·8	1·05
27	7 y	M	0·79	3·8	4·8	74	1·31	0·93	36	2·67	0·4	0·5	1·2	72·7	47·2	1·54	2·0	2·2	0·90
28	7 y	M	0·75	3·5	4·6	75	1·31	0·87	34	2·79	0·5	0·5	1·0	56·5	54·1	1·04	2·7	2·4	1·12
29	7½ y	F	0·86	4·0	4·6	69	1·25	0·89	33	2·74	0·5	0·5	1·0	77·9	62·1	1·25	2·2	1·9	1·15
30	7½ y	M	0·84	3·6	4·3	70	1·28	0·96	33	2·70	0·4	0·5	1·2	58·2	37·0	1·44	2·3	2·4	0·95
31	8 y	M	0·97	3·9	4·0	70	1·28	0·98	33	2·64	0·5	0·6	1·2	60·7	57·0	1·19	2·1	1·9	1·10
32	8½ y	M	0·96	3·6	3·7	80	1·48	0·89	41	2·92	0·5	0·5	1·0	50·9	45·8	1·11	2·4	1·9	1·14
33	9 y	F	0·92	3·7	4·0	69	1·37	1·08	34	2·91	0·5	0·6	1·2	54·5	48·9	1·11	2·8	2·5	1·12
34	9 y	F	0·94	3·7	3·9	81	1·54	1·35	43	2·57	0·6	0·6	1·0	53·4	59·8	0·89	2·5	2·1	1·19
35	10 y	F	1·17	4·1	3·5	77	1·39	1·06	39	2·78	0·5	0·6	1·2	58·7	46·4	1·48	2·6	2·3	1·13
36	11 y	M	1·28	4·5	3·5	78	1·42	0·79	40	2·82	0·6	0·7	1·1	71·2	62·5	1·13	2·7	2·5	1·08
37	11 y	M	1·31	4·2	3·2	76	1·36	0·76	38	2·72	0·6	0·7	1·1	59·2	55·3	1·07	2·8	2·4	1·16
38	12 y	M	1·30	3·3	4·3	78..	1·23	0·80	39	2·40	0·5	0·6	1·2	61/1	45·7	1·33	3·4	3·0	1·13
39	13 y	M	1·35	4·4	3·2	77	1·39	0·97	38	2·80	0·5	0·6	1·2	65·6	46·7	1·40	2·8	2·5	1·12
40	14 y	M	1·46	3·9	2·7	76	1·37	0·91	36	2·69	0·6	0·6	1·0	40·4	42·4	0·95	2·3	2·3	1·00
41	15 y	F	1·46	4·4	3·0	76	1·37	1·05	38	2·80	0·5	0·6	1·2	61·1	43·4	1·40	2·0	2·5	0·80
42	16 y	M	1·59	4·9	3·1	74	1·22	1·02	36	2·50	0·6	0·7	1·1	74·4	58·8	1·26	2·9	2·7	1·07
43	20 y	M	1·70	4·6	2·7	79	1·29	0·86	41	2·53	0·6	0·6	1·0	60·0	50·2	1·19	3·1	3·1	1·00
44	21 y	F	1·60	4·2	2·6	73	1·20	0·87	35	2·79	0·6	0·7	1·1	48·5	45·2	1·07	2·3	2·6	0·88
45	21 y	F	1·42	4·0	2·8	69	1·25	0·85	32	2·55	0·6	0·7	1·1	47·2	46·8	1·00	3·0	2·8	1·07

Abbreviations: BSA = body surface area, Dd = left ventricular end-diastolic dimension, EF = ejection fraction Vcf = mean velocity of circumferential fibre shortening, Vpw = mean normalised posterior wall velocity, %Δs = per cent change in minor axis with systole, MNSER = mean normalised systolic ejection rate, PWd = left ventricular posterior wall thickness at end-diastole, IVS = interventricular septal thickness, IVS/PW ratio = ratio of posterior wall to interventricular septal thickness, EDV = left ventricular end-diastolic volume, LV mass = left ventricular mass, EDV/LV mass ratio = ratio of left ventricular mass to end-diastolic volume, LA = left atrial dimension, Ao = aortic root dimension, LA/Ao ratio = ratio of aortic root dimension to left atrial dimension.

tricular hypertrophy relative to the degree of volume overload to which the left ventricles had been subjected. Even when the 8 patients with large shunt and normal pulmonary artery pressure and the 15 patients with large shunt and pulmonary hypertension were compared separately with normal controls (Table 6), statistical discrimination did not improve, again showing relative lack of left ventricular hypertrophy in ventricular septal defect.

LEFT VENTRICULAR POSTERIOR WALL THICKNESS (PW), INTERVENTRICULAR SEPTAL THICKNESS (IVS), AND IVS/PW RATIO

Posterior wall thickness at end-diastole (PWd) was 0·45 ± 0·09 cm in group 1 and 0·48 ± 0·12 cm in group 2, which was not significantly different. Ventricular septal thickness (IVS) was 0·51 ± 0·11 cm in group 1 compared with 0·61 ± 0·13 cm in

Table 3 *Echocardiographic data from patients with ventricular septal defect (group 2)*

Case no.	*Age*	*Sex*	*BSA* (m^2)	*Dd* (*cm*)	(*cm per* m^2)	*EF*	*Vcf* (*circ/s*)	*Vpw* (s^{-1})	%Δs	*MNSER* (*EDVs/s*)	*PWd* (*cm*)	*IVS* (*cm*)	*IVS/PW ratio*	*EDV* (*ml per* m^2)	*LV mass* (*g per* m^2)	*EDV/LV mass ratio*	*LA* (*cm*)	*Ao* (*cm*)	*LA/Ao ratio*
1	2 wk	M	0·20	1·8	9·0	70	1·85	1·58	33	3·91	0·3	0·3	1·0	30·5	34·5	0·88	1·1	0·9	1·22
2	3 wk	F	0·24	1·6	6·6	68	1·95	1·90	31	4·00	0·3	0·4	1·3	17·9	23·3	0·76	1·3	0·9	1·44
3	5 m	F	0·27	2·0	7·4	72	1·75	1·50	35	3·80	0·5	0·6	1·2	31·0	58·8	0·52	2·1	1·2	1·75
4	6 m	F	0·27	2·0	7·4	72	1·75	1·50	35	3·80	0·4	0·5	1·2	31·0	44·0	0·70	1·6	1·2	1·33
5	6 m	F	0·30	2·9	9·6	80	2·00	1·03	41	4·05	0·4	0·4	1·0	79·3	73·3	1·08	2·7	1·6	1·68
6	8 m	M	0·35	2·8	8·0	77	1·96	1·42	39	4·02	0·3	0·4	1·3	65·7	44·6	1·47	2·2	1·6	1·37
7	1 y 1 m	F	0·50	3·0	6·0	78	1·81	1·35	40	3·56	0·4	0·7	1·7	56·6	46·8	1·20	2·8	1·7	1·64
8	1 y 1 m	M	0·41	2·8	6·8	68	1·58	0·99	28	3·52	0·3	0·4	1·3	56·1	37·0	1·51	2·1	1·6	1·31
9	1 y 5 m	M	0·45	3·1	6·9	71	1·20	0·67	29	2·58	0·3	0·5	1·6	64·9	55·3	1·17	2·5	1·7	1·47
10	1 y 5 m	F	0·50	3·7	7·4	79	1·55	0·83	40	2·99	0·4	0·5	1·2	100·4	69·0	1·45	2·5	1·4	1·78
11	1 y 5 m	M	0·47	3·2	6·8	69	1·56	0·93	31	3·38	0·4	0·6	1·5	72·9	58·0	1·25	2·3	1·7	1·35
12	1 y 5 m	F	0·40	3·7	9·2	72	1·59	0·85	35	3·23	0·4	0·7	1·7	125·5	86·2	1·45	2·6	1·4	1·85
13	1 y 8 m	M	0·58	3·0	5·2	78	1·66	1·38	40	3·26	0·3	0·4	1·3	48·8	30·0	1·62	2·1	1·6	1·31
14	1 y 11 m	F	0·41	3·2	7·8	82	1·98	1·13	43	3·73	0·4	0·6	1·5	83·6	66·3	1·26	2·6	1·7	1·52
15	2 y 3 m	F	0·54	4·1	7·6	71	1·31	0·93	34	2·77	0·4	0·5	1·2	127·2	76·1	1·67	2·7	1·6	1·68
16	2 y 6 m	F	0·63	3·1	4·9	68	1·29	0·80	31	2·79	0·5	0·6	1·2	46·3	51·7	0·89	2·3	1·8	1·27
17	3 y	M	0·62	3·6	5·8	77	1·38	0·99	38	2·76	0·6	0·6	1·2	78·8	71·7	1·10	2·8	2·3	1·21
18	3 y	M	0·52	3·7	7·1	69	1·35	0·79	32	2·91	0·4	0·6	1·5	96·5	66·5	1·45	3·3	2·1	1·53
19	3½ y	M	0·63	3·3	5·2	70	1·19	1·19	33	2·45	0·5	0·7	1·4	56·2	58·0	0·96	2·4	1·9	1·26
20	3½ y	F	0·61	4·2	6·9	70	1·38	0·99	33	2·93	0·4	0·5	1·2	127·2	73·7	1·72	3·2	2·1	1·52
21	3½ y	F	0·59	3·3	5·6	70	1·19	0·86	33	2·45	0·4	0·6	1·5	60·0	47·4	1·26	3·7	2·1	1·76
22	4 y	M	0·67	4·4	6·5	68	1·13	0·87	32	2·20	0·5	0·6	1·2	133·1	94·6	1·40	2·8	1·8	1·55
23	5 y	M	0·70	4·0	5·7	72	1·34	0·89	35	2·78	0·6	0·7	1·1	95·7	94·8	1·00	2·5	2·0	1·25
24	5 y	F	0·71	3·7	5·2	69	1·24	0·83	32	2·41	0·4	0·7	1·7	70·7	48·6	1·45	2·4	2·4	1·00
25	5 y	F	0·72	3·9	5·4	70	1·11	0·76	33	2·29	0·4	0·6	1·5	81·8	53·0	1·54	2·5	1·6	1·56
26	5 y	M	0·68	3·4	5·0	73	1·17	0·88	35	2·43	0·4	0·5	1·2	60·6	44·7	1·35	2·5	2·4	1·04
27	5 y	F	0·68	3·5	5·1	68	1·30	0·87	31	2·74	0·5	0·6	1·2	62·3	59·7	1·04	2·2	1·9	1·15
28	5 y	M	0·71	3·4	4·8	73	1·53	1·17	35	3·12	0·4	0·5	1·2	58·0	42·9	1·35	2·3	2·0	1·15
29	6 y	F	0·72	3·4	4·7	68	1·35	0·98	32	2·99	0·4	0·6	1·5	57·2	42·2	1·35	3·3	2·8	1·17
30	6 y	F	0·68	3·9	5·7	70	1·19	0·91	33	2·45	0·5	0·6	1·2	86·6	72·9	1·14	2·2	1·9	1·15
31	6½ y	F	0·86	3·8	4·4	74	1·41	0·91	36	2·87	0·5	0·7	1·4	66·8	56·5	1·18	3·0	2·1	1·42
32	7 y	M	0·80	4·0	5·0	72	1·25	0·83	37	2·58	0·5	0·6	1·2	83·7	66·6	1·25	3·2	1·9	1·68
33	7 y	M	0·74	4·3	5·8	69	1·08	0·95	32	2·33	0·6	0·7	1·1	107·5	99·6	1·07	2·7	1·9	1·42
34	7½ y	F	0·87	3·8	4·3	74	1·31	0·93	36	2·67	0·5	0·6	1·2	66·1	55·7	1·18	3·0	1·9	1·50
35	7½ y	F	0·74	3·5	4·7	81	1·33	0·80	42	2·50	0·4	0·5	1·2	57·3	41·8	1·37	2·6	2·0	1·30
36	7½ y	M	0·78	3·7	4·7	69	1·29	1·08	32	2·79	0·6	0·6	1·0	64·3	72·0	0·89	2·5	2·1	1·19
37	8½ y	M	1·00	3·9	3·9	70	1·19	0·85	33	2·45	0·6	0·6	1·0	58·9	61·8	0·95	3·8	2·3	1·65
38	9 y	F	0·89	5·3	5·9	68	1·16	0·83	30	2·55	0·5	0·8	1·6	168·6	98·5	1·71	3·2	1·9	1·68
39	9½ y	F	0·94	3·7	3·9	74	1·35	0·96	37	2·74	0·6	0·6	1·0	53·4	59·8	0·89	3·1	2·3	1·34
40	10 y	F	1·19	4·4	3·7	74	1·29	0·81	36	2·65	0·5	0·6	1·2	74·9	53·4	1·40	3·2	2·1	1·52
41	10¾ y	M	1·40	4·8	3·4	69	1·27	0·68	31	2·19	0·6	0·6	1·0	74·3	65·8	1·19	3·6	2·9	1·24
42	11 y	F	1·29	4·0	3·1	72	1·25	1·07	55	2·59	0·6	0·9	1·5	52·7	52·3	1·00	2·4	2·0	1·20
43	11 y	F	1·20	4·3	3·6	80	1·39	0·93	41	2·70	0·8	0·8	1·0	66·3	90·8	0·73	3·6	2·9	1·24
44	11 y	F	1·30	4·3	4·4	77	1·41	0·91	39	2·74	0·6	0·6	1·0	81·0	74·8	1·08	3·5	2·0	1·75
45	12 y	M	1·25	4·1	3·3	74	1·21	0·97	36	2·44	0·5	0·8	1·6	55·0	43·4	1·26	2·8	2·7	1·03
46	13 y	F	1·28	5·3	4·1	75	1·21	0·79	37	2·46	0·8	0·8	1·0	117·3	119·2	0·98	3·4	2·5	1·36
47	13½ y	M	1·48	4·3	2·9	68	1·16	0·95	31	2·47	0·5	0·7	1·4	53·8	41·1	1·30	4·9	3·1	1·58
48	15 y	F	1·34	4·5	3·3	73	1·36	1·08	35	2·84	0·5	0·6	1·2	68·0	48·1	1·41	3·5	3·1	1·12
49	16 y	M	1·26	5·3	4·2	68	1·06	0·78	32	2·24	0·6	0·6	1·0	119·1	85·9	1·38	3·3	2·4	1·37
50	20 y	M	1·65	6·0	3·6	74	1·14	0·62	36	2·33	0·8	0·8	1·0	137·0	117·8	1·16	4·0	2·7	1·48
51	21 y	F	1·60	4·6	2·9	67	0·89	0·81	30	1·95	0·7	1·0	1·4	63·7	64·2	0·99	3·0	3·1	0·96

Abbreviations as in Table 2.

group 2. This resulted in asymmetric septal hypertrophy (IVS/PW ratio > 1·5) in 11 patients in group 2. As shown in Table 7, there was no correlation between the size of the shunt or presence or absence of pulmonary arterial hypertension and asymmetric septal hypertrophy. Though the IVS/PW ratio was abnormal, the actual thickness of the IVS did not exceed the upper limit of normal; it was uniform and showed no bulge at left ventricular outflow tract level. Both the IVS and PWd showed transient but significant increases immediately after operation (group 3) (Table 4), most probably because of surgical manipulation and oedema. These, however, returned to preoperative values later (group 4).

EJECTION FRACTION

There was no significant difference in ejection fraction between groups 1 and 2. Preload is increased in ventricular septal defect because of the large quantity of blood returning from the lungs and afterload is decreased because the high pressure

Table 4 *Changes in 5 patients after surgical closure of ventricular septal defect*

Comparison between preop and 1 week postop (5 cases)	*Preop*	*1 week postop*	*P*
Left atrium/aortic root (LA/Ao) ratio	1·61 ± 0·21	1·28 ± 0·2	<0·05
LV end-diastolic dimension (cm per m^2)	6·3 ± 1·8	5·1 ± 1·3	<0·05
LV end-diastolic volume (ml per m^2)	130·8 ± 23·1	76·3 ± 31·5	<0·05
LV mass (g per m^2)	93·0 ± 6·6	84·6 ± 15·6	NS
Interventricular septal thickness (cm)	0·68 ± 0·08	0·84 ± 0·05	<0·05
Posterior wall thickness (cm)	0·52 ± 0·08	0·64 ± 0·11	<0·05
Ejection fraction (%)	69 ± 2	58 ± 5	<0·05
Mean velocity of circumferential fibre shortening (circ/s)	1·20 ± 0·22	0·92 ± 0·15	<0·05
Relative change in minor axis with systole (%)	32 ± 2	25 ± 3	<0·05
Mean normalised posterior wall velocity (s^{-1})	0·85 ± 0·06	0·99 ± 0·12	<0·05
Comparison between 1 week and 3 weeks postop (5 cases)	*1 week postop*	*3 weeks postop*	*P*
Left atrium/aortic root (LA/Ao) ratio	1·28 ± 0·2	1·19 ± 0·17	NS
LV end-diastolic dimension (cm per m^2)	5·1 ± 1·3	5·0 ± 1·0	NS
LV end-diastolic volume (ml per m^2)	76·3 ± 31·5	76·7 ± 24·0	NS
LV mass (g per m^2)	84·6 ± 15·6	69·1 ± 8·6	NS
Interventricular septal thickness (cm)	0·84 ± 0·05	0·66 ± 0·09	<0·05
Posterior wall thickness (cm)	0·64 ± 0·11	0·54 ± 0·5	<0·05
Ejection fraction (%)	58 ± 5	74 ± 5	<0·05
Mean velocity of circumferential fibre shortening (circ/s)	0·92 ± 0·15	1·35 ± 0·19	<0·05
Relative change in minor axis with systole (%)	25 ± 3	37 ± 4	<0·05
Mean normalised posterior wall velocity (s^{-1})	0·99 ± 0·12	1·02 ± 0·15	NS

Table 5 *Changes in 7 patients before and at 3 or more weeks after surgical closure of ventricular septal defect*

	Before	*After*	*P*
Left atrium/aortic root (LA/Ao) ratio	1·58 ± 0·23	1·16 ± 0·15	<0·05
LV end-diastolic dimension (cm per m^2)	5·7 ± 1·8	4·5 ± 1·1	<0·05
LV end-diastolic volume (ml per m^2)	112·6 ± 37·2	68·4 ± 24·3	<0·01
LV mass (g per m^2)	85·6 ± 14·3	65·8 ± 9·5	<0·01
Interventricular septal thickness (cm)	0·66 ± 0·08	0·66 ± 0·08	NS
Posterior wall thickness (cm)	0·54 ± 0·08	0·57 ± 0·07	NS
Ejection fraction	71 ± 4	75 ± 4	<0·05
Mean velocity of circumferential fibre shortening (circ/s)	1·25 ± 0·20	1·36 ± 0·16	<0·05
Relative change in minor axis with systole (%)	34 ± 3	37 ± 3	<0·05
Mean normalised posterior wall velocity (s^{-1})	0·88 ± 0·06	1·04 ± 0·13	<0·05

Table 6 *Comparisons between normal controls and patients with large ventricular septal defects*

	Normal controls	*Large VSD and normal PAP (8 patients)*	*P*	*Large VSD and pulmonary hypertension (15 patients)*	*P*
Mean velocity of circumferential fibre shortening (circ/s)	1·48 ± 0·22	1·50 ± 0·27	NS	1·40 ± 0·33	NS
LV end-diastolic volume/LV mass ratio	1·16 ± 0·22	1·22 ± 0·35	NS	1·20 ± 0·27	NS

Abbreviations: PAP = pulmonary artery pressure.

left ventricle is emptying through the ventricular septal defect into the low pressure pulmonary circuit. Both these factors will increase ejection fraction, so that even if there were intrinsic depression of myocardial function, this would not be detected by measuring ejection fraction.

RELATIVE CHANGE IN MINOR AXIS WITH SYSTOLE (%ΔS) AND MEAN NORMALISED SYSTOLIC EJECTION RATE (MNSER)

Changes in %Δs and MNSER were similar to changes in ejection fraction. This is not unexpected since the basic echocardiographic measurements, Dd and Ds, are involved in all three determinations.

MEAN VELOCITY OF CIRCUMFERENTIAL FIBRE SHORTENING (Vcf)

Vcf values in group 1 (1·48 ± 0·21 circ/s) were not significantly different from group 2 (1·38 ± 0·26). Even when group 2 was subdivided according to the size of the shunt and presence or absence of pulmonary hypertension, neither the 8 patients with large ventricular septal defect and normal pulmonary artery pressure nor the 15 patients with a large ventricular septal defect and pulmonary arterial hypertension showed a statistically significant difference from group 1 (Table 6). Vcf fell significantly to 0·92 ± 0·15 immediately after operation (group 3) (P < 0·05), but returned to normal later (group 4).

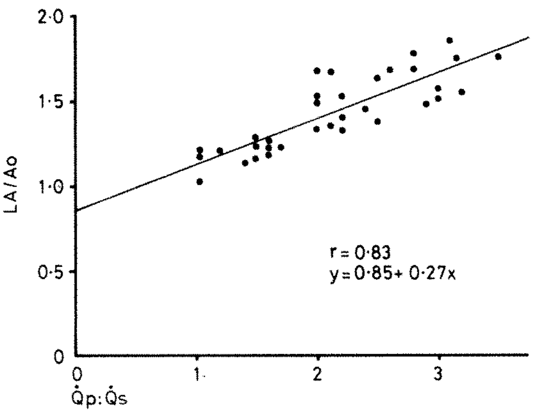


Fig. 3 *Relation between pulmonary/systemic ratio ($\dot{Q}p/\dot{Q}s$) and left atrium/aortic root dimension ratio (LA/Ao) in patients with ventricular septal defect.*

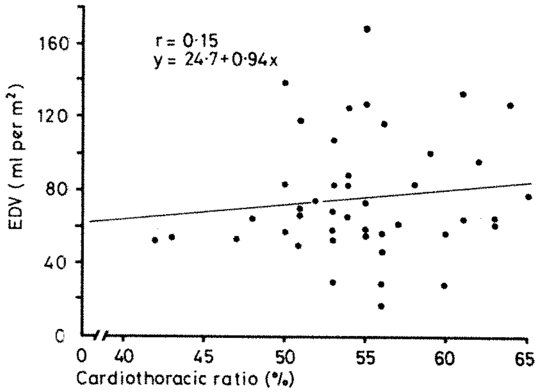


Fig. 4 *Relation between echocardiographic left ventricular end-diastolic volume (EDV) and cardio-thoracic ratio in patients with ventricular septal defect.*

MEAN NORMALISED POSTERIOR WALL VELOCITY (Vpw)

The mean of Vpw in group 1 (1·04 ± 0·18 s^{-1}) was not significantly different from group 2 (0·99 ± 0·25 s^{-1}) though individual patients had lower values.

In contrast to per cent Δs and Vcf, Vpw improved immediately after operation (group 3). This may result from impairment of ventricular septal motion in the immediate postoperative period (Fig. 5) and compensatory increase in left ventricular posterior wall motion, thus normalising left ventricular function.

LEFT ATRIAL DIMENSION (LA)

Although left atrial dimension was significantly increased in group 2 (2·8 ± 0·7 cm) compared with the normal control value (2·2 ± 0·5 cm), there was considerable overlap caused by the variability in left atrial size with age.

AORTIC ROOT DIMENSION (AO)

Determination of aortic root dimension did not show any statistically significant difference between normal controls and patients with ventricular septal defect.

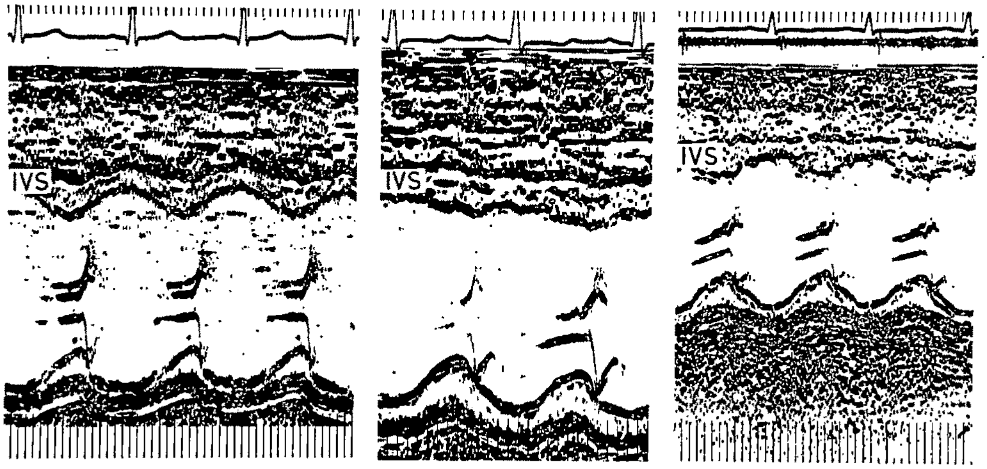
LA/AO RATIO

The mean of LA/Ao ratio was 1·09 ± 0·07 in group 1 and 1·42 ± 0·23 in group 2. The difference between these two groups is highly significant ($P < 0·001$). LA/Ao ratio, therefore, improved the separation between normal subjects and patients with ventricular septal defect by minimising the variability in left atrial size caused by age. Patients

Table 7 *Comparative data of shunt size, pulmonary artery pressure, and asymmetrical hypertrophy of septum*

Case no.	*Age*	*Sex*	*Echo IVS/PW ratio*	*ECG*	*$\dot{Q}p:\dot{Q}s$*	*PAP/SAP*	*Family history of ASH/ HOCM*
1	1 y 1 m	F	1·7	+ 60°, BVH, QII, III, VF, V4-6	2·5:1	0·45	—
2	1 y 5 m	F	1·7	+ 90°, BVH Q V5-6	3·1:1	0·78	—
3	3½ y	F	1·5	+ 90°, BVH, QI, VL, V5-6	2·6:1	0·94	—
4	5 y	F	1·7	+ 30°, BVH, IRBBB, Q in V6 only	3:1	0·84	—
5	5 y	M	1·5	+ 60°, BVH, Q V5-6	Moderate (NC)	(P2 normal)	—
6	5 y	F	1·5	+ 60°, BVH, Q V4-6	Small (NC)	(P2 normal)	—
7	6 y	F	1·5	+ 60°, BVH, Q II, III, VF	1·6:1	0·25	—
8	7 y	M	1·5	− 30°, IRBBB, Q I, VL, V5-6	2:1	0·97	—
9	8 y 2 m	M	1·5	+ 30°, BVH, Q I, VL, V4-6	Small-moderate (NC)	(P2 normal)	—
10	9 y	F	1·6	+ 120°, BVH, Q II, III, VF, V4-6	2·8:1	0·83	—
11	12 y	M	1·6	+ 75°, Q II, III, VF	Small (NC)	(P2 normal)	—

Abbreviations: IVS/PW ratio = ratio of interventricular septum to left ventricular posterior wall, ECG = electrocardiogram, $\dot{Q}p:\dot{Q}s$ = pulmonary/systemic flow ratio obtained at cardiac catheterisation, PAP/SAP = pulmonary artery pressure/systemic artery pressure, ASH = asymmetric septal hypertrophy, HOCM = hypertrophic obstructive cardiomyopathy, BVH = biventricular hypertrophy, IRBBB = incomplete right bundle-branch block, NC = not catheterised, P2 = pulmonary component of second heart sound.



Pre-op 1/52 post-op 3/52 post-op

Fig. 5 *Echocardiogram from a patient with a large ventricular septal defect and pulmonary hypertension showing normal movement of interventricular septum (left), reduced septal movement 1 week after operation (middle), and return to normal pattern 3 weeks after surgical closure (right). IVS = interventricular septum, preop = preoperative echocardiogram, 1/52 and 3/52 post-op = 1 week and 3 weeks after operation.*

with $\dot{Q}p:\dot{Q}s$ ratios of 2:1 or more had LA/Ao ratios more than 1·33 while those with $\dot{Q}p:\dot{Q}s$ less than 2:1 had LA/Ao ratios equal to or less than 1·26. When LA/Ao ratio was related to $\dot{Q}p:\dot{Q}s$, there was very good correlation ($r = 0{\cdot}83$) (Fig. 3). The relation is expressed by the equation: $LA/Ao = 0{\cdot}85 + 0{\cdot}27\,(\dot{Q}p:\dot{Q}s)$. The regression equation may also be expressed as $\dot{Q}p:\dot{Q}s = 2{\cdot}60\,(LA/Ao) - 1{\cdot}56$.

Discussion

Despite an incidence of 2 per 1000 live births (Hoffman, 1968) ventricular septal defect has attracted little attention in papers on echocardiography. At first glance it appears that this congenital anomaly is ideally suited to study by echocardiography but there are technical problems. 'A hole in the septal echo' does not mean anatomical absence of that part of the ventricular septum. This is because the septum may not always be at right angles to the incident ultrasound beam. This would produce apparent absence of the septum even though it were present. Furthermore, there is slight septal rotation with each heart beat in some children and this rotational phenomenon can cause the normal septum to appear to be broken. Finally, the width of the ultrasound beam may be larger than the size of the defect or the edges of the defect may overlap in the plane of examination. In this instance, the examiner will always see the septum and not recognise a slit-like defect (Goldberg *et al.*, 1975). It is not surprising, therefore, that investigators have tended to focus their attention on the secondary haemodynamic effects produced by ventricular septal defect rather than on primary echocardiographic diagnosis.

Large ventricular septal defects cause increased pulmonary blood flow and result in enlargement of left atrium and left ventricle. Left atrial size gives an insight into the magnitude of pulmonary blood flow and has been shown to correlate well with the size of the shunt in ventricular septal defect (Carter and Bowman, 1973). But there is a large normal variability in left atrial size, which results in considerable overlap between normal controls and patients with enlarged left atrium (Brown *et al.*, 1974). Left atrial size is age-dependent but is very variable even when corrected for body surface area. Silverman and associates (1974) indicated the usefulness of expressing left atrial enlargement in terms of LA/Ao ratio. They reported a LA/Ao ratio of 0·86 in premature infants without left-to-right shunt. Later, Brown *et al.* (1974) and Lewis and Takahashi (1976) found ratios of 0·99 and 0·93 in normal adults and children, respectively. Waggoner *et al.* (1976) in a echo-electrocardiographic correlation of left atrial enlargement found that a ratio greater than 1·17 indicated left atrial enlargement. The normal range reported by Popp (1976) was between 0·80 and 1·3. These differences in LA/Ao ratio (mean 1·09 ± 0·07) are partly the result of the differing age and body size of the subjects, but the ratio also depends on whether the diameter of the aortic root was measured at end-systole or end-diastole, and whether left atrial dimension was measured between the anterior edge of posterior aortic wall and the anterior edge of posterior left atrial wall or between the posterior edge of posterior aortic wall and the anterior edge of posterior left atrial wall (Sahn *et al.*, 1976).

In our study, determination of LA/Ao ratio proved useful in distinguishing large from small shunts though further quantification was not possible. There was slight overlap at pulmonary/systemic ($\dot{Q}p:\dot{Q}s$) flow ratios between 1·9:1 and 2:1 but this did not invalidate the value of LA/Ao in separating large from small shunts. All patients with $\dot{Q}p:\dot{Q}s$ of 2:1 or more, as measured at catheterisation, had LA/Ao ratio greater than 1·26 (mean of 1·41 ± 0·23), while LA/Ao was less than 1·26 in patients with $\dot{Q}p:\dot{Q}s$ ratio less than 2:1. There was very good correlation ($r = 0·83$) between LA/Ao and $\dot{Q}p:\dot{Q}s$ ratio, though not as close as that ($r = 0·96$) obtained by Lewis and Takahashi (1976). As would be expected, LA/Ao ratio showed a significant fall after surgical closure of ventricular septal defect in patients in whom both pre- and postoperative data were available.

We have not made serial preoperative echocardiographic assessments of ventricular shunt size though these have been shown to be of clinical value (Meyer *et al.*, 1975). Left atrial and left ventricular size may be affected by changes in pulmonary vascular resistance and by the development of infundibular stenosis. With the help of a pulmonary valve echogram and LA/Ao ratio, it is possible to determine whether a decrease in pulmonary blood flow results from the defect getting smaller or the development of pulmonary vascular disease. Furthermore, right ventricular anterior wall thickness will remain normal if the defect becomes smaller, but will increase if pulmonary vascular disease or infundibular stenosis develops.

Jarmakani *et al.* (1971) reported persistent abnormalities in left ventricular size and pump function in children after surgical closure of a ventricular septal defect at ages ranging from 3 to 12 years. The finding of abnormal volumes led these authors subsequently to investigate pressure-velocity indices of left ventricular contractile state. They confirmed the decrease in left ventricular contractility in patients who before operation had large ventricular septal defects and left ventricular hypertrophy as determined by ventriculography. Recently Cordell and his associates (1976) studied 13 patients who had a ventricular septal defect closed in the first two years of life. They found that left ventricular end-diastolic volume, left ventricular systolic output, and left ventricular mass returned to normal, and that there was no impairment of left ventricular pump function as measured by ejection fraction.

The present study shows a significant increase in left ventricular chamber dimension and left ventricular mass in patients with large ventricular septal defects, though we have no information on patients with pulmonary vascular disease or infundibular stenosis. After surgical closure of the defects, there was a substantial reduction in these measurements though left ventricular mass was still increased. Left ventricular function as measured by ejection phase indices appeared to be unimpaired both preoperatively (group 2) and in 7 patients (group 4) who were studied at 3 to 6 weeks after operation. One of these 7 patients was under 2 years of age. The ages of the other 6 at the time of operation ranged from 4 to 16 years.

The thickness of the left ventricular posterior wall was within normal limits in 23 patients with large ventricular septal defects, despite electrocardiographic evidence of left or biventricular hypertrophy in these subjects. This finding is in agreement with that of Goldberg *et al.* (1975) who rarely found increased left ventricular wall thickness in isolated ventricular septal defect despite the frequent electrocardiographic interpretation of 'left ventricular hypertrophy' in their cases. It is difficult to demarcate the boundary between the ventricular wall and contrast material on ventriculograms. Angiocardiographic measurements of the ventricular wall include overlapping and infolding of trabeculae and papillary muscles and usually substantially overestimate wall thickness (Hugenholtz *et al.*, 1969; Rackley, 1976) and therefore left ventricular mass, since posterior wall thickness is one of the two dimensions (the other being left ventricular end-diastolic dimension) used in the calculation of left ventricular mass. Since the left ventricular mass determined angiocardiographically is increased to a similar extent in pressure and volume overload (Krayenbuehl *et al.*, 1976), estimates of the degree of hypertrophy based on this measurement alone will not give a true picture of the degree of left ventricular hypertrophy. It is, therefore, important to assess hypertrophy in relation to volume overload. When this was done, by calculating the EDV/LV mass ratio in patients with ventricular septal defect, this was not significantly different from the normal control value, suggesting that there was little hypertrophy relative to volume overload.

There are obvious differences between our postoperative studies and those described by Jarmakani *et al.* (1971) and Maron *et al.* (1973): firstly, the postoperative assessment in our patients was early, and second, there was little evidence of left ventricular hypertrophy in relation to the degree of volume overload. It is likely that the absence of significant hypertrophy may have spared these patients a relative myocardial ischaemia that might accompany the hypertrophic process. Finally, we agree with Cordell and co-workers (1976) that the patients who made up Jarmakani's study had their defects closed in early and mid 1960's. They did not have the benefit of present intraoperative techniques which have changed considerably over the past decade with far greater appreciation of the possible permanent effects of myocardial ischaemia produced during intracardiac manipulation. In our patients, like those in Cordell's series, the defects were closed using cardiopulmonary bypass and surface cooling with intermittent cross-clamping of the aorta. As they suggested, it is possible that the intraoperative procedures used in our patients might have served to protect their hearts to a greater extent than was possible 10 years ago, and may have contributed to their better functional status after operation. Determination of ejection phase indices at rest only gave limited insight into contractile behaviour of the myocardium; further assessment of cardiac performance during exercise is important to reproduce more closely the strain of normal daily life.

Although it has been suggested that impairment of left ventricular function persists into the late postoperative period after surgical closure of the ventricular septal defect, there is little information about changes in the immediate postoperative period. Angiographic techniques are unsuitable for repeated studies and are not feasible immediately after open heart surgery. The echocardiogram gives information about left ventricular chamber dimension, left ventricular mass, and left ventricular function, and also direction of septal movement. In 5 patients studied 1 week after operation (group 3), a reduction in left ventricular end-diastolic volume suggested an improvement in left ventricular performance, while the mean velocity of circumferential fibre shortening (Vcf) and relative change in minor axis with systole (%Δs) fell, implying a deterioration in left ventricular performance. Septal motion was either reduced or showed an intermediate pattern. The ejection phase indices and septal movement returned to within the normal limits 3 weeks after surgery. The present study also emphasises difficulties of attempting to quantify left ventricular function in terms of a single index when a number of separate changes are occurring simultaneously. A similar experience was reported by Venco and associates (1976) in patients after corrective operations for aortic regurgitation.

We have thus shown that in patients with large ventricular septal defects, left atrial dimension, left ventricular size, and left ventricular mass were significantly increased. After surgical closure of the defect, there was a substantial reduction in these measurements, though left atrial size and left ventricular mass still remained high. Left ventricular function as measured by ejection phase indices appeared to be unimpaired at rest but the effect of exercise was not investigated.

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Fixed subaortic stenosis
Value of echocardiography for diagnosis and differentiation between various types

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SUMMARY The M-mode echocardiographic and cross-sectional findings in 19 patients with proven fixed subaortic stenosis are described. Based on their haemodynamic, angiocardiographic, and surgical analysis, two main groups of patients were identified. Group 1 consisted of 13 patients with the membranous form of the disease which was further subdivided into patients with a thin membrane and a normal outflow tract (group 1a: 3 patients) and those with a thicker fibrous ring or collar and some degree of outflow tract narrowing (group 1b: 10 patients).

Group 2 consisted of 6 patients with the typical long segment or tunnel form of the disease.

The outflow tract was of a normal size in all 3 patients in group 1a, and an abnormal echo, probably from the subaortic membrane, was seen in only 1 patient on M-mode and cross-sectional images. The narrowed left ventricular outflow tract was diagnosed with both methods in all patients in groups 1b and 2. The area of narrowing extended over a longer segment in the patients in group 2, and this was more easily appreciated from the cross-sectional images.

Premature closure of the aortic valve cusps was recorded in 2 patients in group 1a, 5 in group 1b, and 2 in group 2. It seems from these findings that fixed subvalvular aortic stenosis due to an isolated discrete subaortic membrane cannot reliably be diagnosed by echo. Patients with narrowed outflow tract, however, are reliably detected by echo. The differentiation between a short and a long segment of narrowing is made with more confidence from cross-sectional images.

Fixed subaortic stenosis, a condition causing obstruction to left ventricular outflow, can be produced by an isolated discrete fibrous membrane located just beneath the aortic valve, a thicker fibrous ring or collar which is always associated with some degree of left ventricular outflow tract narrowing, or by diffuse long segment fibromuscular narrowing.

The correct differentiation between these various anatomical forms is important as they involve a different natural history. Furthermore, each type has its specific problems and a different prognosis when operation is considered for symptomatic patients (Maron *et al.*, 1976; Katz *et al.*, 1977). A few studies have indicated that echocardiography could be a helpful and noninvasive means for the diagnosis and the differentiation between the types of fixed subaortic stenosis (Davis *et al.*, 1974; Popp *et al.*, 1974; Roelandt, 1977). In addition, cross-sectional imaging has been proposed as an important method for the evaluation of the left ventricular outflow tract (Weyman *et al.*, 1976).

The purpose of this study was to test both M-mode echocardiography and cross-sectional imaging for their role in diagnosing and differentiating the different types in 19 patients with proven subaortic stenosis.

Subjects and methods

Nineteen patients with fixed subaortic stenosis were included in this study. There were 8 men and 11 women (ages: 14 to 60 years: median 20). Major complaints were inappropriate exertional dyspnoea in 18, chest discomfort during exercise in 12, and dizziness, faintness, and/or syncopal attacks in 3.

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Table 1 *Clinical features of 19 cases with fixed subaortic stenosis*

Case no.	*Age (y), sex*	*Cath. findings + angio*	*Surgical findings*	*Assoc. lesions*
Group 1a				
1	17 M	LV-Ao: 115 mmHg; AR: + +	Thin membrane	
2	19 M	LV-Ao: 106 ,, ; AR: + +	,, ,,	
3	11 M	LV-Ao: 90 ,, ; AR: + +	,, ,,	Bicuspid Ao
Group 1b				
4	57 F	LV-Ao: 100 ,, ; AR: –	– – – –	– – – –
5	58 F	LV-Ao: 41 ,, ; AR: + +	– – – –	– – – –
6	38 F	LV-Ao: 80 ,, ; AR: –	Thickened septum	Small membrane
7	20 M	LV-Ao: 23 ,, ; AR: +	– – – –	– – – –
8	20 M	LV-Ao: 80 ,, ; AR: +	– – – –	– – – –
9	20 M	LV-Ao: 60 ,, ; AR: +	Membrane	– – – –
10	50 F	LV-Ao: 60 ,, ; AR: +	Membrane	– – – –
11	14 F	LV-Ao: 105 ,, ; AR: + +	Membrane	– – – –
12	20 F	LV-Ao: 110 ,, ; AR: + +	Membrane	LVH
13	18 M	LV-Ao: 90 ,, ; AR: + + +	Membrane	Thick IVS + thick Ao valve
Group 2				
14	19 M	LV-Ao: 60 ,, ; AR: +	Membrane LVOT ?	
15	60 F	LV-Ao: 80 ,, ; AR: +	Tunnel SAS	
16	20 F	LV-Ao: 100 ,, ; AR: –	– – – –	
17	42 F	LV-Ao: 60 ,, ; AR: –	Tunnel	Thick septum
18	20 F	LV-Ao: 80 ,, ; AR: + +	Tunnel + thick septum	
19	30 F	LV-Ao: 130 ,, ; AR: + +	Abnormal mitral valve	

None had signs of heart failure at the time of their examination. Based on the haemodynamic, angiocardiographic, and surgical findings, patients were divided into 2 main groups (Table 1).

Group 1: 13 patients had the membranous form of the disease. Three had a normal left ventricular outflow tract (group 1a) whereas the other 10 had different degrees of left ventricular outflow tract narrowing over a short segment (group 1b).

Group 2: 6 patients with the long segment or tunnel type of subaortic stenosis.

HAEMODYNAMIC, ANGIOCARDIOGRAPHIC, AND SURGICAL DATA (TABLE 1)

Group 1

The diagnosis of fixed subaortic stenosis in the 13 patients of this group was mainly based on the demonstration of a significant pressure gradient between the left ventricular cavity and the left ventricular outflow tract. A distinct membrane with a subvalvular chamber beneath the aortic valve was shown in only 7 patients on the left ventricular cineangiocardiogram, in the right anterior oblique projection. In 11 patients, aortic regurgitation was seen during supra-aortic valve angiography. Nine patients were operated on. In 3, a thin subaortic membrane attached to the anterior mitral valve leaflet was found and excised; in the other 6 patients, there was a thicker membranous collar with a circumference of 2 to 5 cm just beneath the aortic valve, and this was excised as completely as possible. A bicuspid aortic valve was described in 1 patient and no further information on the aortic valve was available in the surgical reports. Severe concentric hypertrophy of the left ventricle was mentioned in 1 and a thickened interventricular septum in 2 patients.

Group 2

All 6 patients had a severe systolic pressure gradient across the left ventricular outflow tract. In 4 patients, the long segment narrowing of the left ventricular outflow tract was diagnosed from the left ventricular cineangiocardiogram. Aortic regurgitation was present in 4. Five patients were operated upon. Myectomy was performed in 3, myotomy in 1, and a left ventricular outflow tract reconstruction in the fifth one, who died after operation.

ULTRASONIC EXAMINATION

The apparatus used was a commercially available instrument (EchocardioVisor 03), which has both M-mode and cross-sectional imaging facilities (Roelandt, 1977). From the standard transducer position on the chest (Roelandt, 1977), several M-mode scans were made with a transducer scanning speed as constant as possible. Patients were examined in the supine or slightly left lateral recumbent position. During the examination, gain settings were continuously adjusted for best visualisation of cardiac structures. Recordings were made with a Honeywell line scan recorder (Visicorder 1856) on light sensitive paper (Kodak Linagraph, 1892). The following indices were studed on the M-mode recordings: width of the outflow tract at end-systole, motion of the aortic valve cusps, the presence of a high frequency vibration on the anterior mitral valve leaflet during diastole, and the systolic motion pattern and contraction pattern of the left ventricular walls (obliteration of left ventricular cavity during systole in the area beyond the posterior papillary muscles). Cross-sectional studies were performed in the long axis sagittal plane following the left ventricular outflow tract and recorded on videotape.

During the analysis, special attention was paid to the width and the length of narrowing of the left ventricular outflow tract, the presence of left ventricular hypertrophy, and apical left ventricular cavity obliteration during systole.

Table 2 *Echocardiographic findings in 19 patients with fixed subaortic stenosis*

Group	*1a*	*1b*	*2*
No. of patients	3	10	6
Narrow LVOT M-mode	—	10	6
Narrow LVOT 2D	—	'ridge' like	Long segment
Thin 'extra' echo	1	—	—
Early closure Ao cusps	2	5	2
Flutter Ao cusps	—	4	3
AI	—	5	1
Concentric LVH	—	8	2
ASH	—	2	2
SAM	—	1	1
Apical obliteration	—	5	2

Table 3 *Left ventricular outflow tract width, septal and posterior wall thickness in 19 cases with fixed subaortic stenosis*

Case No.	*LVOT* (*mm*)	*IVS* (*mm*)	*LVPW* (*mm*)	*Ratio IVS/LVPW*
1	20	13	13	1·0
2	21	12	12	1·0
3	20	13	13	1·0
4	17	18	12	1·54
5	9	18	18	1·0
6	10	20	10	2·0
7	18	18	18	1·0
8	4	16	16	1·0
9	10	15	15	1·0
10	17	15	15	1·0
11	11	16	16	1·0
12	10	18	18	1·0
13	11	15	15	1·0
14	10	18	18	1·0
15	8	18	18	1·0
16	10	14	14	1·0
17	12	22	13	1·6
18	8	20	15	1·3
19	10	16	16	1·0

LVOT, width in mm of left ventricular outflow tract at end-systole; IVS, interventricular septal thickness (mm) at end-diastole; LVPW, left ventricular posterior wall thickness (mm) at end-diastole.

Echocardiographic results (Tables 2 and 3)

GROUP 1A

In only 1 of the 3 patients, was an abnormal echo seen in the left ventricular outflow tract (Fig. 1)

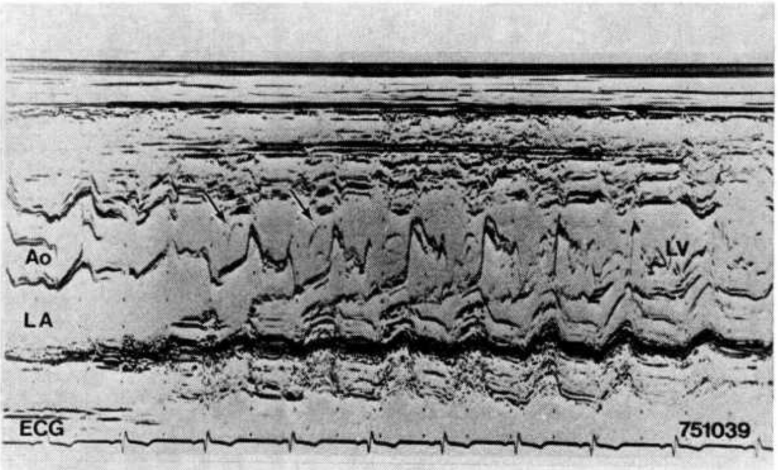


Fig. 1 *Echocardiogram of a patient with fixed subaortic stenosis (group 1a). A membrane was found and excised at operation. Note the normal size of the left ventricular outflow tract and the discrete echoes of membrane (see arrows). Because the membrane is attached to the mitral valve, the systolic motion pattern of that valve is abnormal. The aortic valve (Ao) cusps move normally.*

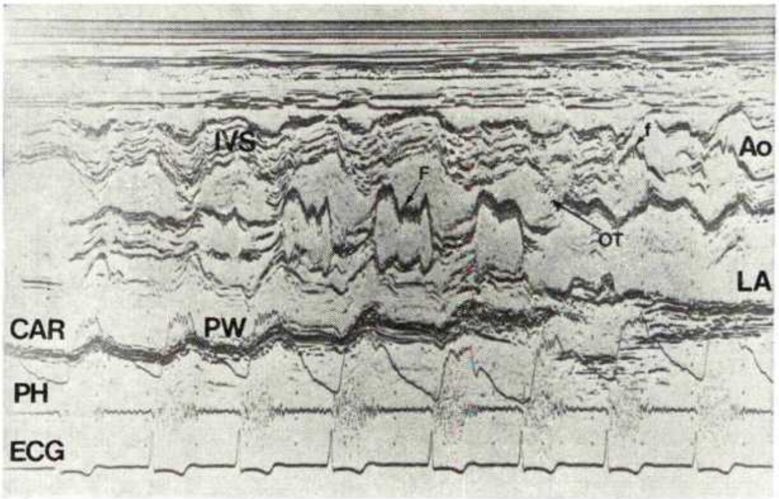


Fig. 2 *M-mode scan from the aorta (Ao) to the apex of the left ventricle in a patient in group Ib. The end-systolic width of the left ventricular outflow tract (OT) is narrowed over a short segment. A high frequency diastolic flutter (F) on the anterior mitral valve leaflet, suggestive of aortic regurgitation, is seen. The aortic valve cusps show premature closure in mid-systole, and a systolic flutter (f) on the aortic cusps is noted. The interventricular septum (IVS) and LV posterior wall (PW) are both symmetrically hypertrophied. CAR, carotid artery tracing; PH, phonocardiogram.*

and this was probably a membrane. The size of the left ventricular outflow tract was larger than 20 mm in all 3 patients. Premature closure of the aortic cusps was seen in 2 patients. No specific abnormalities could be detected on cross-sectional images.

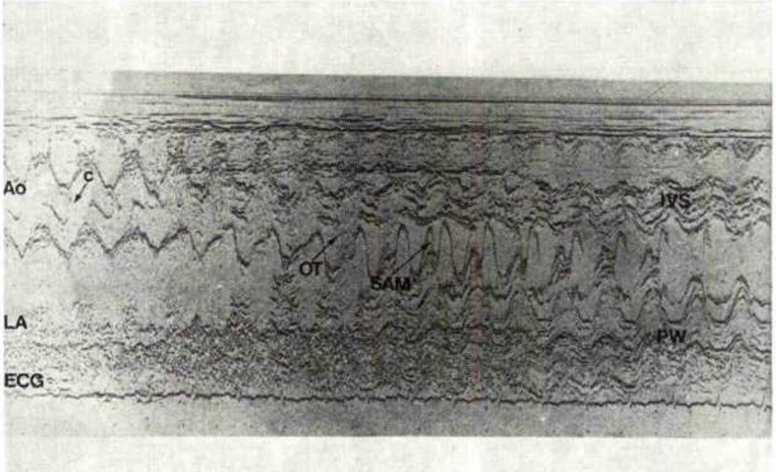
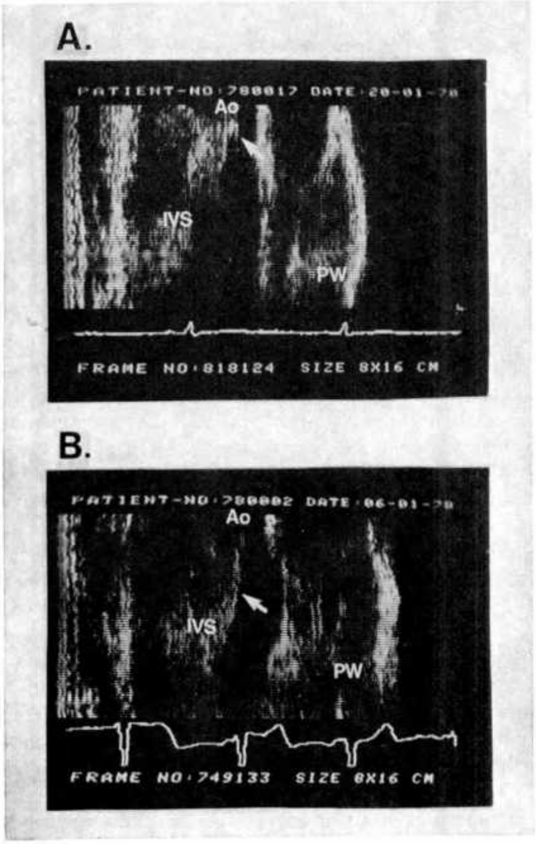


Fig. 3 *M-mode scan in a patient in group Ib. All features pointing to fixed subaortic stenosis are seen on this echocardiogram. In addition, the anterior mitral leaflet shows an abnormal systolic anterior motion (SAM) (see arrow), indicative of a dynamic obstruction to left ventricular outflow. OT, outflow tract; C, closure.*

GROUP 1B

All 10 patients in this group had an end-systolic left ventricular outflow tract width of less than 20 mm (range 10 to 18 mm; normal value ⩾ 20 mm) (Fig. 2). Five patients had an initial rapid opening of at least one cusp of the aortic valve followed by an abrupt closure shortly after the onset of ventricular ejection. In 4 of these, a distinct systolic fluttering of the aortic cusps was also recorded. A high frequency diastolic fluttering on the anterior mitral valve leaflet, suggestive of aortic regurgitation (Winsberg *et al.*, 1970), was seen in 5 patients.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Ao
IVS
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FRAME NO:818124 SIZE 8X16 CM
B.
PATIENT-NO:788802 DATE:06-01-78
Ao
IVS
PW
FRAME NO:749133 SIZE 8X16 CM

Fig. 4 (*A*) *Ultrasonic cross-sectional image of the patient whose M-mode sector scan is described in Fig. 2. A narrow left ventricular outflow tract is observed, over a short segment (see arrow), appearing as a 'ridge' just beneath the aortic valve cusps.*
(*B*) *Ultrasonic cross-sectional image of the patient whose M-mode sector scan is described in Fig. 5. A narrow left ventricular outflow tract is observed over a long segment from a level just beneath the aortic cusps to the level of the mitral valve leaflets at left ventricular mid-cavity. For abbreviations see text.*

Concentric left ventricular hypertrophy was present in 8, and 1 of them had an abnormal systolic anterior motion of the anterior mitral valve leaflet (Fig. 3). Asymmetric septal hypertrophy was present in 2 patients with end-diastolic septal thicknesses of 18 and 20 mm, respectively. Systolic apical obliteration was seen in 5 patients. On cross-sectional images, a short-segment narrowing of the left ventricular outflow tract which appeared as a 'ridge' just below the aortic valve was diagnosed in all (Fig. 4A). Severe concentric left ventricular hypertrophy was present in 8 patients, 5 of whom had systolic obliteration. In these patients, the papillary muscles were displaced more anteriorly in the left ventricular cavity. The left ventricle had an abnormal shape in 2 patients, similar to the left ventricular shape seen in patients with genetic asymmetric septal hypertrophy.

GROUP 2

All 6 patients showed a long narrow left ventricular outflow tract on their M-mode recordings, which was quite distinctive from the echocardiographic pattern seen in patients of group 1b (Fig. 5). Two patients showed an early aortic cusp closure and 3 systolic flutter. A diastolic mitral valve pattern consistent with aortic regurgitation was seen in 1 patient, and 2 had severe concentric left ventricular hypertrophy (end-diastolic septal and posterior left ventricular wall thickness 18 mm and 18 mm, respectively), one of whom had systolic anterior motion. Two patients showed apical obliteration in addition to concentric left ventricular hypertrophy. Two patients had disproportionate septal thickening (septal to free posterior wall ratio 1·3 and 6, respectively). On their cross-sectional images, all 6 had narrowed left ventricular outflow tracts over a considerable length which extended almost to the mid-cavity level of the left ventricle (Fig. 4B). The severe concentric left ventricular hypertrophy present in 2 patients resulted in a small cavity and systolic obliteration (Fig. 6).

Discussion

Two major types of subvalvular aortic stenosis are described: the type with fixed obstruction and the type with functional obstruction to left ventricular outflow. Distinct echocardiographic abnormalities are present in the latter form (Henry *et al.*, 1973).

The fixed form of subaortic stenosis can be divided into a membranous type, either isolated or associated with left ventricular outflow tract narrowing, and the tunnel type of subaortic stenosis. Special attention has been given in recent studies to the different prognosis and clinical

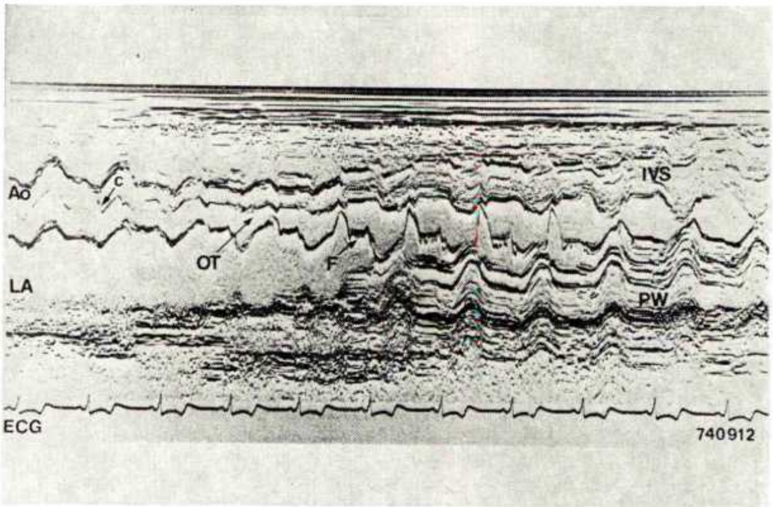


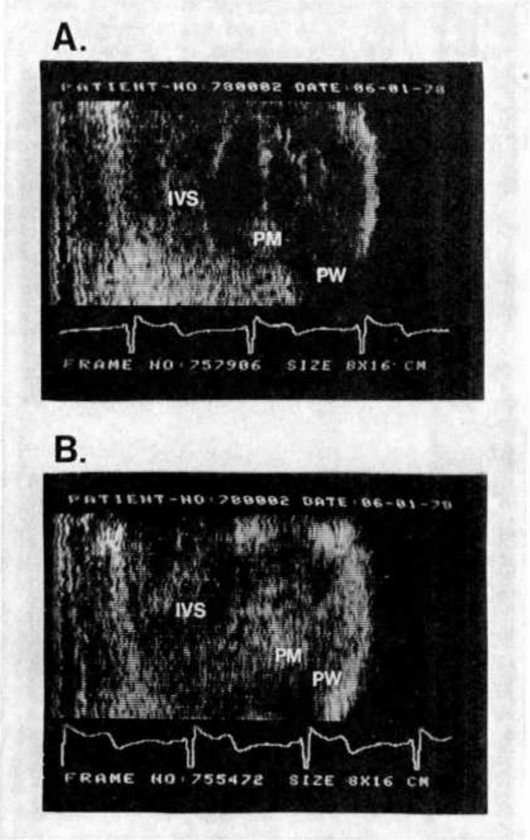
Fig. 5 *M-mode scan from the aorta (Ao) to the apex of the left ventricle performed with a uniform transducer speed in a patient in group 2. Note the length of the narrowed left ventricular outflow tract (OT) (see arrow). For abbreviations see text.*

management for the different types of fixed subaortic stenosis. A high incidence of sudden death has been observed in the tunnel type, and surgery should not be recommended to these patients because of the risk and the lack of symptomatic improvement (Maron *et al.*, 1976; Katz *et al.*, 1977). However, surgical management of the membranous form is relatively safe and effective, though not always totally corrective (Kelly *et al.*, 1972). Accurate diagnosis of the type of fixed subaortic stenosis is important. The diagnosis is often based on pressure recordings demonstrating a subvalvular gradient, since angiocardiography may fail to show the membrane or to visualise the narrowed left ventricular outflow tract. This was the case in 6 patients in our group 1 and 2 patients of group 2.

It should be recognised, however, that the quality of the angiocardiograms and especially the incidence of the *x*-ray beams are of major importance. This was not always satisfactory in our series. A positive and uniquivocal visualisation with ultrasound of an isolated subvalvular membrane is also rare, since the subaortic diaphragm was diagnosed in only 1 patient of group 1a. In a study of 11 patients, Lundström (1977) was not able to demonstrate the membrane in any of them. This is probably because the ultrasound beam is not easily aimed in a direction to hit this structure perpendicularly. With the exception of this uncommon type of the disease our findings suggest that a narrow left ventricular outflow tract can reliably be diagnosed from echo. Therefore, echocardiography may play a major role in the diagnosis and differentiation between the different types of the disease and should be performed in all patients with left ventricular outflow disease, before haemodynamic and angiographic analysis is considered. The combination of a narrow left ventricular outflow tract, early closure of the aortic cusps, the presence of aortic regurgitation and concentric ventricular hypertrophy with small cavity is suggestive if not diagnostic of the membranous form associated with narrow left ventricular outflow tract (see Fig. 2).

The tunnel form of fixed subaortic stenosis can also be missed on the cineangiocardiogram (cases 14 and 19) but was always detected by echocardiographic examination, and is best appreciated from cross-sectional images. This is because the left ventricular outflow tract can be thought of as a flattened space in these cases. The echocardiographic beam probably passes through the small dimension of the tunnel, whereas the *x*-ray beams in the anteroposterior projection are perpendicular to the tunnel, resulting in visualisation of the large dimensions of the tunnel on the angiogram (Roelandt and van Dorp, 1977).

Early systolic closure and fluttering of one of the aortic valve cusps, earlier described as characteristic of fixed subaortic stenosis (Davis *et al.*, 1974), has not been found to be sensitive for detecting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PM
PW
FRAME NO 757906 SIZE 8X16 CM
B.
PATIENT-NO 788882 DATE 06-01-78
IVS
PM
PW
FRAME NO 755472 SIZE 8X16 CM

Fig. 6 *(A) Ultrasonic transverse cross-sectional image at the level, just beneath the mitral leaflets at end-diastole.*
The cavity of the left ventricle is well seen. The interventricular septum (IVS) and left ventricular posterior wall (PW) are symmetrically hypertrophied. (B) Same cross-section as described in Fig. 6A at end-systole. Observe the systolic obliteration of the left ventricular cavity. PM, papillary muscle.

it in our series. This finding is now recognised to be a nonspecific echocardiographic abnormality (Weyman *et al.*, 1976). There was a striking discrepancy between echocardiographic abnormalities of the mitral valve suggesting aortic regurgitation and the angiocardiographic findings. Only 6 patients were diagnosed from echo while 15 of the 19 patients had minor degrees of aortic regurgitation on their cineangiocardiograms. This discrepancy could be explained by differences in direction of the regurgitant jet. Asymmetric septal hypertrophy and an abnormal systolic anterior motion of the anterior mitral leaflet, features typically associated with idiopathic subaortic stenosis, also occur in fixed subaortic stenosis. This is important when operation is considered, and, in addition to excision of the fixed obstruction, a septal myotomy–myectomy should be performed. Otherwise, the patient may succumb in the immediate postoperative period.

The coexistence of asymmetric septal hypertrophy, systolic anterior motion of the mitral valve leaflet, and fixed subaortic stenosis suggests an interrelation between this type of subaortic stenosis and more diffuse functional types of left ventricular outflow obstruction. The history and echocardiographic study of family members of 2 patients (cases 8 and 17) showed first degree relatives with typical features of idiopathic hypertrophic subaortic stenosis, confirmed at cardiac catheterisation. A relation between the membranous form of fixed subaortic stenosis and tunnel subaortic stenosis has also been suggested (Kelly *et al.*, 1972). This is further substantiated by the observation in one of our patients (case 14) who developed the typical form of tunnel subaortic stenosis after excision of a subaortic collar 10 years previously. Some authors believe in an age-related incidence of this disease (Katz *et al.*, 1977). Many patients die in adolescence suddenly or as a result of intractable heart failure. However, 4 of our patients were older than 50 years, which has rarely been described.

In conclusion, it appears that echocardiography is a useful noninvasive means for the diagnosis of fixed subaortic stenosis, except for the form where there is an isolated membrane in a left ventricular outflow tract of normal size. The echo diagnosis of fixed subaortic stenosis is not always specific and may involve several investigations on M-mode recordings and cross-sectional images. The method certainly allows a better preoperative evaluation and hence surgical management. Echocardiography will also enlarge our knowledge of the natural history of fixed subaortic stenosis.

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Management of unstable angina at rest by verapamil

A double-blind cross-over study in coronary care unit

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SUMMARY A therapeutic trial with verapamil, a calcium-antagonist drug, was performed in 12 patients admitted to our coronary care unit because of frequent daily attacks of angina at rest attributed to coronary vasospasm. After a 48-hour run-in period, oral verapamil 480 mg/day and placebo were administered alternately during 4 randomised 48-hour periods. Transient ischaemic attacks with ST segment elevation or depression, with or without pain, were documented by continuous electrocardiographic monitoring. The number of attacks during the run-in and 2 placebo periods were 128, 123, and 130, respectively, and 31 and 23 during the 2 treatment periods ($P < 0.006$ and $P < 0.003$). This drug therefore appears to be effective in the management of patients with frequent attacks of angina at rest.

Although various forms oı medical and surgical treatment have been proposed for the management of unstable angina at rest, the results are inconclusive (Cairns *et al.*, 1976) and often conflicting (Conti *et al.*, 1973; Bertolasi *et al.*, 1974; Hultgren, 1976; Selzer *et al.*, 1976; Clark *et al.*, 1977). This may be because the patients are selected on purely clinical criteria, rather than on criteria based on the pathogenetic mechanisms responsible for the onset of the anginal attacks; this method of selection leads to an inhomogeneous group of patients and treatment that is not rational. Rational therapy depends on recognition of the causes of the anginal attacks rather than on the clinical picture alone, which though it has prognostic significance has no clear pathogenetic implications.

Recent studies indicate that in patients with angina at rest, characterised by ST segment elevation or depression, the onset of the attacks cannot be attributed to an increase in the haemodynamic determinants of myocardial oxygen consumption (Guazzi *et al.*, 1971, 1975b; Maseri *et al.*, 1975a, b). In these patients myocardial scintigraphic studies have shown a massive transmural reduction of myocardial tracer uptake during the attacks, associated with ST segment elevation (Maseri *et al.*, 1976; Parodi *et al.*, 1978) or a diffuse or ill-defined reduction of tracer uptake during episodes of angina at rest with ST segment depression (Severi *et al.*, 1977). This reduction of myocardial perfusion appears to be related to either: (1) severe vasospasm of a major coronary branch, when the perfusion deficit is transmural and the ST segment is elevated, or (2) less severe spasm or a spasm of a small branch or spasm in the presence of collaterals, when reduction of perfusion is not transmural and the ST segment is depressed (Marzilli *et al.*, 1977; Maseri *et al.*, 1977b; Parodi *et al.*, 1977).

Beta-blockers and coronary bypass surgery, which are the most commonly adopted therapeutic approaches (Cairns *et al.*, 1976), may not be the rational treatment in those patients with proven vasospastic angina with the clinical characteristic of 'unstable' angina at rest or of 'crescendo' angina.

In preliminary clinical trials we had the impression that verapamil[1], a calcium-antagonist with relaxing properties on large coronary arteries (Golenhofen and Lammel, 1972; Haeusler, 1972), was effective in reducing the number of anginal attacks in those patients. Hence we decided to undertake a double-blind cross-over study with this drug on patients having continuous electrocardiographic monitoring in a coronary care unit (CCU).

Subjects and methods

PATIENTS

We studied 12 patients (34 to 70 years old, average 54 years) admitted to our CCU because of recurrent, frequent daily episodes of angina at rest, which began from 3 months to 10 days before admission.

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[1] Isoptin-Knoll AG, West Germany.

Table 1 *Physical, clinical, electrocardiographic, coronary arteriographic, and myocardial scintigraphic characteristics of patients*

Case no.	*Age (y)*	*History*		*Electrocardiogram*
		Onset of symptoms	*Exercise tolerance*	*Basal*
1	61	1 month (rest)	Good	Negative T V2-V5
2	70	10 days (rest)	Good	0·5 mm ST ↓ V4-V6
3	49	2 months (rest and effort)	Moderate	Negative T II, III, aVF
4	63	1 year (effort) 3 months (rest)	Moderate	Normal
5	61	6 years (effort) 10 days (rest)	Poor	Negative T I, II, III, aVF, V3-V6
6	60	7 months (effort) 1 month (crescendo)	Poor	Nondiagnostic (documented anterior and posterior infarcti in previous tracing)
7	38	1 month (rest)	Good	Negative T I, II, aVL, V1-V2
8	50	2 months (rest)	Good	Normal
9	34	3 months (rest and effort)	Moderate	Incomplete RBBB and LAH
10	63	3 years (effort) 1 month (rest)	Poor	Q II, III, aVF, 0·5 mm ST ↓ V4-V6 I, aVL
11	48	3 months (effort) 1 month (rest)	Moderate	Negative T V1-V4
12	53	1 month (crescendo) 9 months (rest)	Good	Negative T V1-V4, aVL

LMS, left main stem; LAD, left anterior descending; LCA, left circumflex artery; LMB, left marginal branch; LDB, left diagonal branch; RCA, right coronary artery; RBBB, right bundle-branch block; LAH, left anterior hemiblock.
- - - - Not performed.

We excluded from the study patients with anginal episodes of long duration (more than 10 to 15 minutes).

The main physical, clinical, and electrocardiographic characteristics of the patients, the results of coronary angiography, and of thallium-201 myocardial scintigraphic studies are reported in Table 1. Two had had a documented old myocardial infarction, 7 and 25 months before admission. None had a history or clinical signs of congestive heart failure on admission. The electrocardiographic abnormalities during the anginal attacks were ST segment elevation in 6 patients, ST segment depression in 4, and alternate episodes of ST segment elevation and depression in the same leads in 2. Seven patients had in addition asymptomatic episodes of ST segment changes similar to those accompanied by pain. Coronary arteriography was performed by the Judkins technique (1968) in 9 patients. In 6 patients in whom contrast injections could be made during an anginal attack, coronary artery spasm was shown angiographically. The attack occurred spontaneously in 2 and was induced by ergonovine in the other 4. In 1 patient the ergonovine test (0·2 mg in 2 doses of 0·05 mg and 0·15 mg at 10-minute intervals) was negative, while the other 2 did not consent to the test. A massive reduction of myocardial perfusion during a spontaneous anginal attack was documented in all the 8 patients in whom thallium-201 could be injected at the beginning of an ischaemic episode. In 3 patients no direct evidence of a sudden reduction of myocardial blood supply was obtained, as the appropriate studies could not be performed because of failure of the equipment or lack of isotope. However, these patients had no history of effort angina, and repeated measurements of heart rate and systemic blood pressure at the very beginning of the ST segment changes or before the onset of pain failed to show any consistent change relative to control state. No haemodynamic change was observed at the onset of pain in the 3 patients (cases 9, 10, and 11) in whom left ventricular pressure was continuously monitored (Chierchia *et al.*, 1977).

DESIGN OF INVESTIGATION

Following the diagnostic evaluation, the 12 patients selected were kept in the CCU throughout the trial with continuous electrocardiographic monitoring of the lead showing the most obvious changes during the anginal attacks. After a 2-day control period on diazepam (2 to 5 mg 3 times daily), they entered the trial. This was composed of 4 2-day treatment periods, according to the following double-blind cross-over plan:

			Coronary arteriography		*Myocardial scintigraphy*
spontaneous attacks	*Exercise*	*Asymptomatic episodes*	*Control*	*During angina*	*Location of cold areas during ischaemia at rest*
T V2-V5	Positive T V2-V5	No	----	----	----
ST ↓ V4-V6	----	Yes	----	----	----
-V4 ↑ -V4 ↓ III, aVF ↑	2 mm ST ↓ V2-V5	Yes	75% LAD 75% LCA	LAD, LCA spasm	Anteroseptal, inferior
-V5 ↑	3 mm ST ↑ V2-V4	Yes	50% + 75% LAD 50% RCA	LAD spasm	Anterior
ST ↓ I, II, III, aVF	----	No	----	----	Anterior
ST ↓ V2-V6	3 mm ST ↓ V2-V6	No	90% LMS 75% LAD 90% 1° LDB 75% LMB	----	Anterior, inferior posterior
VL ↑ V1-V3	----	No	90% LAD	----	----
VL ↑ V2-V6	Normal	Yes	90% LAD 75% 2° LDB 50% LCA	LAD spasm	
-V5 ↑ -V6 ↓	3 mm ST ↓ V2-V6	Yes	90% LAD	LAD incomplete spasm	Anteroseptal
ST ↓ V4-V6	----	No	75% LAD 100% LCA 100% RCA	----	Anterolateral
-V4 ↑	2 mm ST ↑ I, aVL	Yes	75% LAD 75% LMB	LAD spasm	Anteroseptal
-V4 ↑ LAH	Positive T V1-V3	Yes	90% LAD 100% RCA	LAD spasm	Anterior

Treatment A_1: verapamil (80 mg) 1 tablet every 4 hours for 2 days (480 mg/24 h)
Treatment B_1: placebo 1 tablet every 4 hours for 2 days
Treatment A_2: verapamil (80 mg) 1 tablet every 4 hours for 2 days (480 mg/24 h)
Treatment B_2: placebo 1 tablet every 4 hours for 2 days.

The two sequences of treatments A_1, B_1, A_2, B_2 or B_1, A_1, B_2, A_2 were randomised. Each period of treatment was started at 6 a.m.

During the whole period of the trial the paramedical CCU personnel were instructed to record the monitored lead during each episode of ST segment change and, whenever possible, a 12-lead electrocardiogram. Blood pressure was recorded every 4 hours and heart rate every 2 hours during periods free of ischaemic episodes and whenever

Table 2 *Number of episodes per hour during run-in (C), treatment (A_1, A_2), and placebo periods (B_1, B_2)*

Case no.	*C*		A_1		B_1		A_2		B_2	
1	5	2	0	0	1	1	0	0	1	1
2	2	3	0	2	1	2	0	0	3	3
3	3	3	2	0	7	4	1	0	2	8
4	6	8	0	4	0	4	0	0	0	5
5	1	3	0	0	0	2	0	0	3	1
6	1	2	0	0	3	2	1	1	2	4
7	4	4	1	3	6	1	1	0	1	5
8	8	6	0	1	4	18	5	0	8	7
9	23	6	1	1	20	11	4	0	14	21
10	4	7	0	0	7	5	4	0	7	7
11	10	4	1	3	6	6	1	0	7	8
12	5	8	2	10	6	6	2	3	10	2
Total in 24 hours	72	56	7	24	61	62	19	4	58	72
Total in 48 hours	128		31		123		23		130	
			$P < 0·006$				$P < 0·003$			

there were ST segment changes. Serum enzymes (LDH, CK, SGOT (AST)) and creatinine, haemoglobin and blood count, chest *x*-ray films, standard electrocardiogram, and body weight were obtained every fourth day.

The patients were informed that neither the rationale nor the effectiveness of treatment of this syndrome were yet established and that, given the large spontaneous variability in the frequency of symptoms, the choice of a drug for long-term treatment would require objective demonstration of its efficacy. All gave their written consent to the trial.

A statistical evaluation of the significance of the results was carried out by the Wilcoxon matched-pair signed-rank test (Snedecor and Cochran, 1964).

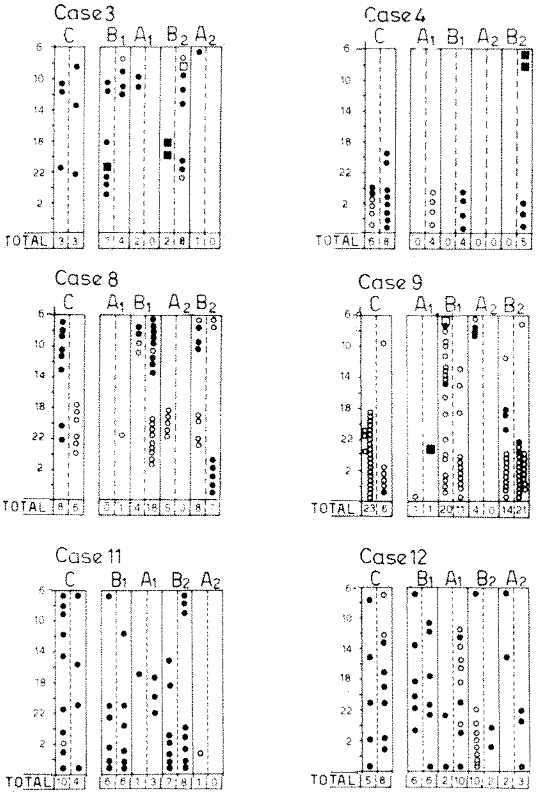

Fig. 1 *Number, type, and time of occurrence of ischaemic episodes in 6 patients. C indicates run-in period; A_1 and A_2 treatment periods; B_1 and B_2 placebo periods. The broken line divides each 2-day period into 2 24-hour periods. Circles and squares indicate episodes with ST segment elevation and depression respectively; closed and open symbols indicate symptomatic and asymptomatic ischaemic episodes respectively. The time (from 0600 hrs) is shown on the scale on the left of each set of data.*

Results

During the trial symptomatic and asymptomatic episodes of ST segment elevation or depression were recorded and were pooled in the statistical analysis. For each patient the total number of ischaemic attacks during the control, treatment, and placebo periods is reported in Table 2. Detailed results of the trial in the 12 patients are presented in Fig. 1 and 2.

No episodes were observed during both periods of treatment in 2 patients and during 1 of the 2 periods in 4. All the others except case 12 consistently showed an obvious reduction in the number of episodes.

For the group as a whole, the number of episodes during the 48-hour run-in period was not statistically different from that during the placebo periods (128 versus 123 and 130). By contrast, during each period of verapamil treatment, a highly significant reduction in the number of episodes was observed (31 and 23, $P < 0{\cdot}006$ and $P < 0{\cdot}003$). The reduc-

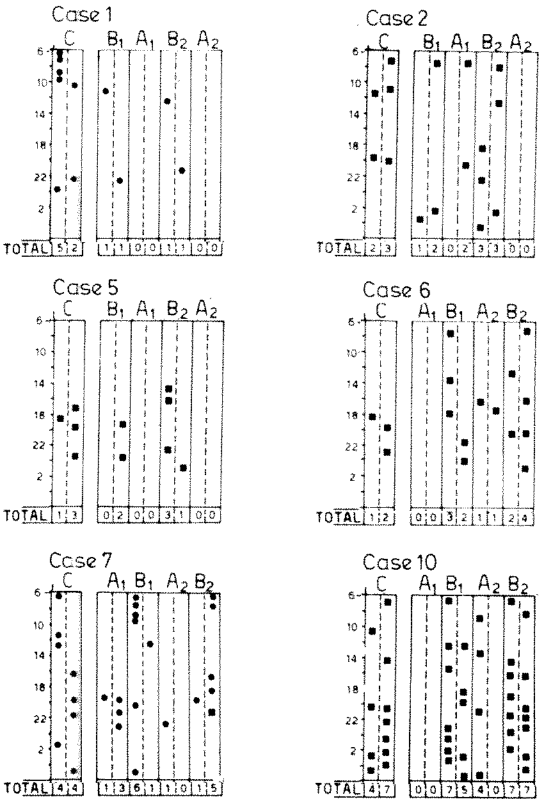

Fig. 2 *Results of the trial in the other 6 patients (shown as in Fig. 1).*

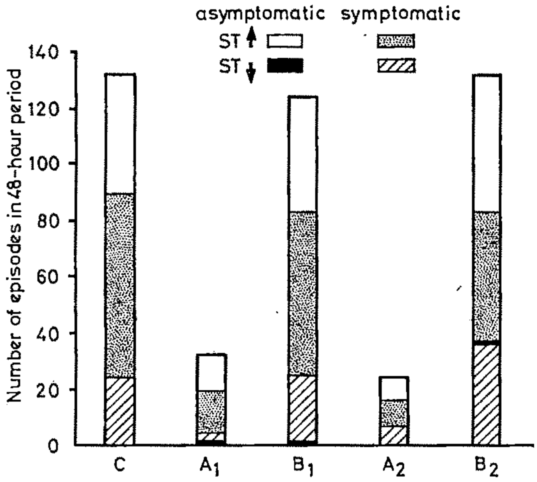

Fig. 3 *The total number of episodes in 12 patients in each 48-hour period of the trial. C indicates run-in period; A_1, A_2 verapamil periods; B_1, B_2 placebo periods. Control and placebo periods show similar number and type of ischaemic episodes, while during treatment with verapamil there is a conspicuous reduction in frequency of all types of episodes.*

tion was similar for the number of episodes with ST segment elevation and depression and for symptomatic and asymptomatic episodes (Fig. 3). Within each period the number of episodes during the first 24 hours was never significantly different ($P < 0·05$) from that observed during the second 24 hours.

There were no consistent changes in heart rate (average of 12 daily measurements) or length of PQ interval, and no conduction disturbances were observed. No significant biochemical changes occurred. A slight reduction of arterial blood pressure (average of 4 daily measurements) was seen in 2 patients (cases 2 and 10) with mild systolic hypertension (Table 3).

SIDE EFFECTS

Muscle cramps and weakness were observed in case 10, constipation in cases 1 and 10, and transitory mental confusion in case 5.

FOLLOW-UP OF PATIENTS

All patients were maintained on verapamil (320 to 400 mg/day). One patient (case 7) had a small myocardial infarct in hospital after completion of the trial, while on verapamil (80 mg 3 times a day) and oral nitrates. Eight patients were discharged free of symptoms; the others had occasional anginal attacks (from 1 to 3 episodes per week). During follow-up (average 47 weeks), 7 patients were free of pain, 3 showed a reduction in the number of ischaemic attacks (cases 3, 4, and 6) (average 2 attacks/week); the follow-up of the last 2 patients is still in progress.

Discussion

Patients categorised clinically as unstable angina at rest constitute a heterogeneous group. Some with extremely limited exercise tolerance develop angina with any minimal increase of myocardial metabolic demand; in others with normal or variably reduced exercise tolerance, the anginal episodes at rest are caused by transient coronary vasospasm. Of all patients with angina at rest, those with extremely reduced coronary reserve (class IV angina pectoris of the Canadian Cardiovascular Society (Crochet *et al.*, 1975)) are a relatively small number. In fact, patients with 'variant' angina, for whom vasospasm can be con-

Table 3 *Effects of verapamil on blood pressure, heart rate, and PQ interval, and side effects*

Case no.	*Blood pressure (mmHg)*				*Heart rate (beats/min)*		*PQ interval (s)*		*Side effects*
	Placebo		*Verapamil*		*Placebo*	*Verapamil*	*Placebo*	*Verapamil*	
	S	*D*	*S*	*D*					
1	120	75	125	75	60	57	0·20	0·22	Constipation
2	175	100	160	100	56	62	0·20	0·20	
3	150	100	135	85	59	58	0·16	0·16	
4	140	85	145	85	72	75	0·14	0·14	
5	110	70	115	70	73	69	0·14	0·18	Transitory mental confusion
6	130	80	130	80	64	62	0·20	0·22	
7	120	85	140	85	82	72	0·20	0·22	
8	130	85	130	80	69	68	0·12	0·12	
9	125	70	120	75	86	65	0·12	0·14	
10	170	90	150	90	76	74	0·14	0·15	Constipation, muscle cramps
11	120	80	115	80	75	77	0·18	0·20	
12	125	85	120	80	76	71	0·16	0·16	

sidered a 'proven hypothesis' (Meller *et al.*, 1976), are found to be a sizeable fraction of those with angina pectoris at rest if appropriately searched for (Maseri *et al.*, 1977a, b). In addition, vasospasm has also been shown to be a cause of angina at rest with ST segment depression in patients with a variable degree of coronary atherosclerosis (Marzilli *et al.*, 1977; Maseri *et al.*, 1977a). Finally, it has been shown by continuous ambulatory electrocardiographic monitoring that the majority of patients with 'stable' angina have ischaemic episodes at rest or at considerably lower work loads than can be achieved during an exercise test; it was suggested that in these patients functional impairment of coronary blood supply capable of causing these anginal attacks may be superimposed (Schang and Pepine, 1977). The evaluation of the effectiveness of drugs on vasospastic angina is thus of practical interest.

There were several reasons for believing that anginal attacks at rest in our group of patients were not caused by an increase of myocardial demand: (1) Five patients had no history of exertional angina; of these 1 had a normal electrocardiographic stress test and 2 developed electrocardiographic signs of ischaemia only at high work loads; (2) in 3 patients continuous haemodynamic monitoring showed that no consistent increase of heart work preceded the onset of the ischaemic episodes; (3) in all patients systematic measurements of blood pressure and heart rate during asymptomatic electrocardiographic ischaemic episodes or at the onset of ST segment changes showed no consistent increase relative to the control periods.

Direct evidence for a vasospastic origin of the attacks was obtained in 9 patients: by both angiography and by myocardial scintigraphy in 5, by myocardial scintigraphy alone in 3, and by angiography alone in 1. In the other 3 patients there was no history of exertional angina, and no consistent increase in heart rate or blood pressure at the onset of anginal attacks. Two had typical 'variant' angina. Thus, all these patients appear to have a common mechanism responsible for the onset of their anginal attacks at rest, which cannot be attributed to an increase of myocardial metabolic demand beyond their coronary reserve. Though we cannot exclude other so far unidentified mechanisms, it is reasonable to infer that their attacks were caused by coronary vasospasm, in spite of the difference in the time of onset of angina, the extent of coronary atherosclerosis, and type of electrocardiographic ST segment change during ischaemia.

The study was carried out in the CCU both because of the severity of the patients' symptoms and because in this environment treatment could be closely supervised and an objective unbiased record obtained of the response to treatment. We selected patients who were having several anginal episodes per day and studied 2 treatment periods alternating with 2 placebo periods, with the aim of comparing the extent and the consistency of the response of the individual patients with that of the group as a whole. We selected 48-hour periods, because of the 2 to 3 hour half-life in blood of the drug after its oral administration (Schomerus *et al.*, 1976), and because of possible carry-over effects of the drug. Longer periods of treatment were not adopted in view of the frequent spontaneous waxing and waning of the disease. We chose a higher than usual dose of the drug in order to overcome possible differences in absorption and to be reasonably certain that an adequate blood level was attained.

A non-parametric test was selected for the statistical evaluation of the results because of the possible lack of homogeneity of response among patients, as it should tend to reduce the influence of a few exceptional responders.

PREVENTION OF ISCHAEMIC EPISODES

A study of Fig. 1 and 2 shows that verapamil appears to be consistently effective in reducing the number of ischaemic episodes in patients in whom angina was predominantly associated with ST segment elevation, in those with angina and ST segment depression, and in those with asymptomatic ST segment changes. The reduction was more obvious in the patients with frequent episodes during the placebo periods. We could not find an explanation for the inconsistent effects observed in case 12 but have previously observed in a trial of intravenous isosorbide dinitrate (Maseri *et al.*, 1976; Distante *et al.*, 1978) that in some patients it is not possible to prevent ischaemic attacks completely, probably because of the very acute phase of their disease.

In the group as a whole, the reduction in number of ischaemic episodes during verapamil treatment was highly significant. Therefore, this drug seems to have a potent effect in preventing attacks of vasospastic angina. Because of the design of our trial (randomised, short-term, cross-over), it is not possible to compare our results with those obtained in other trials with less sophisticated experimental designs (Papazoglov, 1971; Guazzi *et al.*, 1975a). The remarkable effects of verapamil during this trial appear to be maintained during long-term treatment of these patients, with doses of 80 mg 3 to 5 times a day. In fact their course so far appears very favourable, considering the severity of their symptoms initially and the severity of their coronary atherosclerotic disease. Although the number of patients studied is small and the average duration of follow-up is relatively short, the results of this treatment compare favourably with the results reported in similar types of patients of coronary bypass surgery (Miller *et al.*, 1973; Gaasch *et al.*, 1974; Heng *et al.*, 1976) and of other surgical procedures such as cardiac denervation or autotransplantation which have been performed in selected patients with proven coronary vasospasm (Clark *et al.*, 1977).

In conclusion, verapamil is an effective drug for the management of those patients in whom unstable angina at rest is not the result of an excessive increase of myocardial metabolic demand.

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Effects of tocainide on left ventricular performance at rest and during acute alterations in heart rate and systemic arterial pressure

An echocardiographic study[1]

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SUMMARY To determine if the new antiarrhythmic agent tocainide depresses left ventricular function we performed a double-blind cross-over trial of tocainide and placebo in 10 patients with valvular heart disease and recorded echocardiograms (a) in the basal state, (b) during atropine-induced increases in heart rate, and (c) during acute pressure loading with phenylephrine. The drug doses were 400 mg every 8 hours for 3 days, and the mean tocainide plasma concentration in the tocainide group was 5·3 μg/ml.

Except after atropine when there was a slightly higher mean systolic blood pressure in the tocainide group than in the placebo group (mean blood pressure difference 7 mmHg, $P < 0.02$) heart rates and systolic blood pressures for both groups were closely matched during these pharmacological interventions. For the placebo and tocainide groups mean heart rates increased after atropine by 27 and 26 beats/minute, respectively, and during infusion of phenylephrine (when no significant heart rate slowing occurred) mean blood pressures rose by 51 mmHg in the placebo group (to 175 ± 6 mmHg) and by 45 mmHg in the tocainide group (to 176 ± 6 mmHg). During tocainide administration mean velocity of circumferential fibre shortening (mean VCF) in the basal state averaged 1·29 ± 0·06 diam/s. This increased to 1·39 ± 0·08 diam/s with atropine (NS) and then declined to 1·17 ± 0·09 diam/s during infusion of phenylephrine ($P < 0.01$ vs atropine). No significant differences were found when the corresponding values during placebo were compared with these values. Similar directional changes occurred in the average mean posterior wall velocity (mean VPW) during tocainide administration when the corresponding values were 0·75 ± 0·05, 0·87 ± 0·07 ($P < 0.05$), and 0·71 ± 0·05 ($P < 0.01$ vs atropine) s^{-1}, respectively. Again placebo values did not differ significantly from tocainide values.

Thus, in patients with valvular heart disease tocainide in the dose employed has no significant depressant effect on left ventricular function either in the basal state or during acute alterations in heart rate or blood pressure. These data suggest that tocainide can be used safely for antiarrhythmic therapy in patients with mild to moderate left ventricular dysfunction.

Recent reports of animal (Duce *et al.*, 1973; Coltart *et al.*, 1974) and human studies (McDevitt *et al.*, 1976; Winkle *et al.*, 1976; Woosley *et al.*, 1977; Ryan *et al.*, 1978) indicate that an oral analogue of lignocaine, tocainide, is effective in suppressing ventricular arrhythmias and is a promising new antiarrhythmic agent. However, high doses of tocainide in anaesthetised dogs have been shown to depress left ventricular function (Coltart *et al.*, 1974). To determine whether tocainide similarly depresses myocardial function in man we administered typical therapeutic doses of the drug to patients with organic heart disease, and using ultrasound assessed left ventricular function at rest and during acute alterations in heart rate and systemic arterial pressure.

Patients and methods

Ten patients without clinical evidence of coronary artery disease but with known heart disease formed

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Table 1 *Clinical data*

Case no.	*Age (y) and sex*	*Diagnosis*	*Functional class (NYHA classification)*	*Treatment*
1	52F	MR	II	Digoxin
2	40M	Prolapsing mitral leaflet	I	—
3	32F	Prosthetic aortic valve	II	Warfarin, oral contraceptives
4	62M	AR, mild MR	II	Digoxin
5	43F	MR, MS	II	Digoxin, propranolol
6	32F	AS, AR	I	—
7	54F	MR	I	—
8	68M	AR	II	Triamterene, hydrochlorothiazide, glyceryl trinitrate
9	24M	PS	I	—
10	23M	AR	I	—

MS, mitral stenosis; MR, mitral regurgitation; AS, aortic stenosis; AR, aortic regurgitation; PS, pulmonary stenosis.

the study group (Table 1). Their ages ranged from 23 to 68 years, with a mean of 43 years. All were in sinus rhythm. Control echocardiograms were first performed to familiarise the patients with the procedure, the personnel, and the surroundings. Each patient then underwent two echocardiographic studies one week apart. One study followed treatment with tocainide, the other treatment with placebo, and the order was double-blind. The drugs were administered in a dose of 400 mg every 8 hours for the 3 days before each study and all routine medications were continued. The code was not broken until the study was completed and the echocardiograms had been analysed.

An identical procedure was followed during both studies. Initial inquiry was made regarding possible drug-related sensitivity, a 12-lead electrocardiogram was recorded, urine was collected for analysis, an intravenous infusion of 5 per cent dextrose and water was begun, and a blood sample was obtained to evaluate haematological, hepatic, and renal function as well as plasma tocainide concentration and, thus, patient compliance. When the pulse rate and blood pressure (cuff sphygmomanometer) were stable for at least 30 minutes an echocardiogram was recorded. Subsequently atropine was administered intravenously in a quantity sufficient to raise the heart rate approximately 30 beats/minute or until 1·5 mg had been given. When the heart rate and systemic arterial pressure were stable for at least 5 minutes another echocardiogram was obtained. As previously described (Hirshleifer *et al.*, 1975; Crawford *et al.*, 1976), a solution of phenylephrine (40 mg/l) was then infused over 5 to 10 minutes in a quantity sufficient to raise the systolic arterial pressure approximately 40 to 50 mmHg. With the heart rate response to increased arterial pressure blocked by atropine a final echocardiogram was obtained. The infusion was then terminated. The total volume of fluid used in a study was never more than 70 ml. During the second study a deliberate attempt was made to match the heart rate and blood pressure responses with those of the first study.

All patients gave informed written consent to the study procedure which was approved by the Committee on Investigations/Activities Involving Human Subjects, University of California, San Diego. Three of the 10 patients experienced mild adverse reactions while taking tocainide. These symptoms consisted of nausea in one, dizziness in one, and a brief cold sweating episode in one. Two additional patients with withdrawn from the study because of more severe side effects caused by tocainide. One experienced severe nausea and vomiting, and the other rigors. No patient had side effects while taking placebo.

Patients with coronary artery disease or congestive cardiomyopathy were not included in the study because of the concern that raising their heart rates and systemic arterial pressures might be deleterious. We recognise that the choice of patients with valvular heart disease, especially those with mitral and aortic regurgitation, could have affected our results, especially since increases in heart rate and blood pressure may have opposing effects on the beat-to-beat magnitude of regurgitation. Nevertheless, the statistical method we employed, that is, using each patient as his or her own control during the repetition of an identical procedure, should exclude any bias in the results due solely to changes in haemodynamics.

Echocardiograms were recorded with a Picker ultrasonoscope using a 2·5 MHz transducer focused at 7·5 cm. Recordings were made on a Honeywell Visicorder, model 1856, at a paper speed of 100 mm/s. An electrocardiogram and an indirect carotid arterial pulse tracing were recorded simultaneously with the echocardiogram. The patients were studied in the partial left lateral decubitus position. The 'standard intercostal space' technique was employed to obtain reproducible echocardiograms of the endocardial surface of the left ventricle at the level of the chordae tendineae (Popp *et al.*, 1975). Left ventricular dimensions were measured between the endocardial surfaces of the posterior wall and the left side of the septum (Fig. A). The end-diastolic dimension (EDD) was measured at the peak of the R wave of the electrocardiogram. The end-systolic dimension (ESD) was measured before the dicrotic notch on the carotid arterial pulse tracing at the point on the echocardiogram where

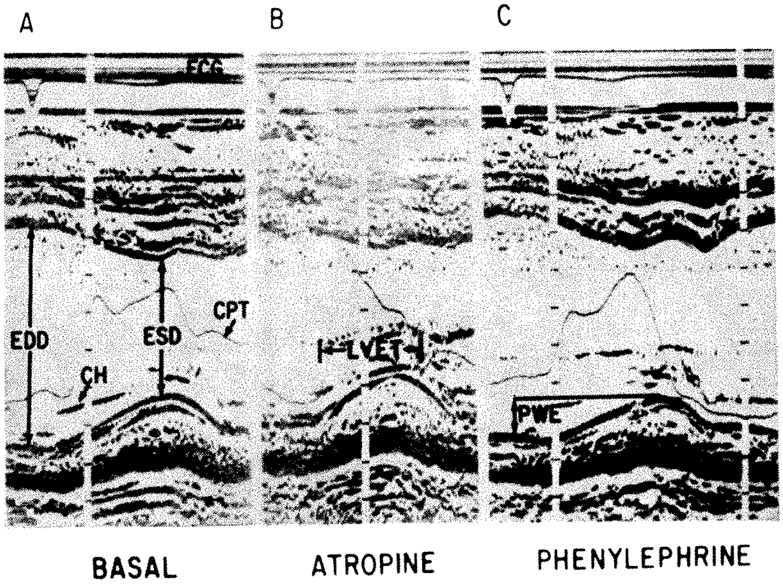

Fig. *Echocardiographic recordings during tocainide therapy. (A) Basal state echocardiogram. For the beat illustrated values were: mean VCF, 1·20 diam/s; mean VPW, 0·75 s^{-1}; left ventricular ejection time 321 ms. The heart rate was 65 beats/min. EDD, end-diastolic dimension; ESD, end-systolic dimension; CH, chordae tendineae; CPT, carotid arterial pulse tracing; ECG, electrocardiogram. (B) After administration of atropine the heart rate increased to 95 beats/min, mean VCF increased to 1·31 diam/s, and mean VPW increased to 0·88 s^{-1}. Left ventricular ejection time (LVET) decreased to 261 ms. (C) During phenylephrine administration the systolic arterial pressure increased by 60 mmHg, and the heart rate fell to 85 beats/min. Mean VCF decreased to 0·95 diam/s, mean VPW decreased to 0·49 s^{-1}, and LVET increased to 340 ms. PWE, posterior wall excursion during systole.*

the perpendicular distance between the endocardial surfaces was smallest. The left ventricular ejection time (LVET) was measured from the indirect carotid arterial pulse tracing (Fig. B).

The mean normalised velocity of circumferential fibre shortening (mean VCF [diam/s]) was calculated as:

$$\frac{\text{EDD} - \text{ESD}}{\text{EDD} \times \text{LVET}} \quad [1]$$

The mean normalised posterior wall velocity (mean VPW [s^{-1}]) was calculated as:

$$\frac{\text{PWE}}{\text{EDD} \times \text{LVET}} \quad [2]$$

where PWE = total excursion of the posterior wall endocardium during systole (Fig. C). All calculations were made using the average of at least 3 cardiac cycles. For data reduction a repeated measures analysis of variance was used (Winer, 1971).

Results

Individual patient data are detailed in Tables 2-4. During tocainide the mean heart rate in the basal state was 61 ± 2 (SE) beats/min. This increased to 87 ± 6 beats/min after atropine ($P < 0·01$). During phenylephrine infusion the mean heart rate fell slightly to 81 ± 5 beats/min (NS vs atropine). Mean heart rates during placebo administration were not significantly different from these values.

The mean systolic arterial pressure in the basal state was 123 ± 6 mmHg during placebo and 131 ± 5 mmHg during tocainide ($P < 0·01$). After atropine these values were 124 ± 6 mmHg (placebo) and 131 ± 5 mmHg (tocainide) ($P < 0·02$). These values were not significantly different from the respective values in the basal state. During infusion of phenylephrine the mean systolic blood pressures for the placebo and tocainide groups were 175 ± 6 mmHg and 176 ± 6 mmHg, respectively (NS). The phenylephrine-induced increases in systolic blood pressure, which averaged 51 mmHg (range 28 to 88 mmHg) during placebo and 45 mmHg (range 32 to 79 mmHg) during tocainide, differed significantly from values after atropine (P < 0·01).

The average mean VCF in the basal state after tocainide was 1·29 ± 0·06 diam/s. Though this increased to 1·39 ± 0·08 diam/s after atropine, the results did not reach statistical significance. During the phenylephrine infusion the average mean VCF decreased to 1·17 diam/s (P < 0·01 vs atropine, NS vs basal state). Placebo values were not significantly different from these.

Table 2 *Effects of oral tocainide on blood pressure and heart rate in basal state and after atropine and phenylephrine*

Case no.	*State*	*Systemic systolic blood pressure (mmHg)*		*Heart rate (beats/min)*	
		Placebo	*Tocainide*	*Placebo*	*Tocainide*
1	Basal	158	156	58	62
	At	160	158	78	78
	Ph	194	195	79	68
2	Basal	106	110	55	60
	At	114	112	95	90
	Ph	142	144	94	90
3	Basal	112	128	62	63
	At	125	125	99	95
	Ph	165	165	95	82
4	Basal	150	150	71	70
	At	145	150	87	84
	Ph	194	194	83	82
5	Basal	108	134	59	61
	At	98	133	66	69
	Ph	186	182	63	63
6	Basal	119	122	49	47
	At	110	122	102	102
	Ph	160	161	128	112
7	Basal	118	127	67	61
	At	118	122	71	71
	Ph	166	166	75	75
8	Basal	118	128	53	50
	At	123	127	77	68
	Ph	198	206	60	57
9	Basal	119	116	51	65
	At	119	118	82	85
	Ph	161	161	81	82
10	Basal	120	138	65	67
	At	124	142	98	125
	Ph	184	185	79	99
Mean basal		123	131	59	61
SEM		6	5	2	2
P		< 0·01		NS	
Mean At		124*	131*	86‡	87‡
SEM		6	5	4 6	6
P		< 0·02		NS	
Mean Ph		175‡§	176‡§	83†‡	81†‡
SEM		6	6	6	5
P		NS 20		NS	

Basal, basal state; At, after atropine; Ph, during pressure loading with phenylephrine; SEM, standard error of the mean; P, significance level; vs, versus; NS, not significant; * not significant vs basal state; † not significant vs atropine; ‡ P < 0·01 vs basal state; § P < 0·01 vs atropine.

Table 3 *Effects of oral tocainide on left ventricular dimensions and ejection time during acute alterations in heart rate and blood pressure*

Case no.	*State*	*EDD (cm)*		*ESD (cm)*		*LVET (ms)*	
		Placebo	*Tocainide*	*Placebo*	*Tocainide*	*Placebo*	*Tocainide*
1	Basal	6·55	6·23	3·75	3·55	281	277
	At	6·39	6·21	3·70	3·44	249	259
	Ph	6·24	6·25	3·86	3·83	256	269
2	Basal	4·87	4·96	3·06	3·18	334	320
	At	4·94	5·05	3·47	3·49	261	267
	Ph	5·24	5·18	3·70	3·70	299	286
3	Basal	4·13	4·07	2·11	2·28	330	293
	At	3·92	3·76	2·01	2·13	247	242
	Ph	4·04	4·10	2·33	2·47	285	270
4	Basal	7·33	7·30	4·49	4·67	319	307
	At	7·15	7·27	4·37	4·80	297	288
	Ph	7·31	7·26	4·85	4·92	334	323
5	Basal	4·85	5·02	3·16	3·37	293	315
	At	4·65	4·88	2·97	3·21	276	294
	Ph	5·03	5·16	3·69	3·62	325	330
6	Basal	5·79	5·59	3·16	3·23	373	380
	At	4·88	4·70	2·81	2·85	267	273
	Ph	4·59	4·89	2·75	3·03	265	285
7	Basal	6·14	6·24	3·19	3·20	316	312
	At	6·10	5·97	3·37	3·48	308	308
	Ph	6·18	6·20	3·19	3·28	305	297
8	Basal	5·48	5·70	2·87	3·28	342	351
	At	4·63	4·89	2·82	2·99	273	305
	Ph	5·55	5·47	3·58	3·67	345	368
9	Basal	5·57	5·70	3·53	3·51	315	302
	At	5·11	5·66	3·33	3·58	281	278
	Ph	5·56	5·79	3·92	4·08	303	301
10	Basal	5·69	5·67	3·52	3·45	323	310
	At	4·70	4·71	3·05	2·99	264	219
	Ph	6·00	5·95	4·07	3·93	341	293
Mean basal		5·64	5·65	3·28	3·37	323	317
SEM		0·29	0·27	0·20	0·18	8	9
P		NS		NS		NS	
Mean At		5·24**	5·31**	3·19*	3·32*	272‡	273‡
SEM		0·31	0·31	0·20	0·21	6	9
P		NS		NS		NS	
Mean Ph		5·57*¶	5·63*¶	3·59**§	3·65**§	306*¶	302*¶
SEM		0·29	0·28	0·22	0·21	10	10
P		NS		NS		NS	

Basal, basal state; At, after atropine; Ph, during pressure loading with phenylephrine; SEM, standard error of the mean; P, significance level; vs, versus; NS, not significant; * not significant vs basal state; ** P < 0·05 vs basal state; ‡ P < 0·01 vs basal state; § P < 0·01 vs atropine; ¶ P < 0·05 vs atropine; EDD, end-diastolic dimension; ESD, end-systolic dimension; LVET, left ventricular ejection time.

Table 4 *Effects of oral tocainide on ultrasound measures of left ventricular performance in basal state and during acute alterations in heart rate and blood pressure*

Case no.	*State*	*Mean VCF (diam/s)*		*Mean VPW* (s^{-1})	
		Placebo	*Tocainide*	*Placebo*	*Tocainide*
1	Basal	1·52	1·56	1·01	0·94
	At	1·69	1·72	1·11	1·12
	Ph	1·49	1·44	0·96	0·97
2	Basal	1·11	1·12	0·60	0·64
	At	1·14	1·16	0·66	0·59
	Ph	0·99	1·00	0·52	0·62
3	Basal	1·48	1·40	1·05	1·04
	At	1·97	1·79	1·37	1·22
	Ph	1·49	1·47	1·11	1·04
4	Basal	1·22	1·17	0·71	0·68
	At	1·31	1·18	0·76	0·71
	Ph	1·01	1·00	0·58	0·56
5	Basal	1·19	1·16	0·94	0·91
	At	1·31	1·16	0·99	0·96
	Ph	0·82	0·90	0·58	0·66
6	Basal	1·22	1·11	0·67	0·60
	At	1·59	1·44	0·78	0·62
	Ph	1·51	1·33	0·88	0·71
7	Basal	1·52	1·56	0·81	0·64
	At	1·45	1·35	0·77	0·88
	Ph	1·59	1·59	0·76	0·78
8	Basal	1·39	1·21	0·72	0·65
	At	1·43	1·27	0·88	0·88
	Ph	1·03	0·89	0·57	0·58
9	Basal	1·16	1·27	0·75	0·68
	At	1·24	1·32	0·88	0·76
	Ph	0·97	0·98	0·59	0·56
10	Basal	1·18	1·26	0·74	0·74
	At	1·33	1·67	0·91	1·10
	Ph	0·94	1·16	0·49	0·63
Mean basal		1·30	1·29	0·80	0·75
SEM		0·05	0·06	0·05	0·05
P			NS		NS
Mean At		1·44*	1·39*	0·91**	0·87**
SEM		0·08	0·08	0·07	0·07
P			NS		NS
Mean Ph		1·17*§	1·17*§	0·70*§	0·71*§
SEM		0·10	0·09	0·07	0·05
P			NS		NS

Basal, basal state; At, after atropine; Ph, during pressure loading with phenylephrine; SEM, standard error of the mean; P, significance level; vs, versus; NS, not significant; * not significant vs basal state; ** P < 0·05 vs basal state; § P < 0·01 vs atropine. Mean VCF, mean velocity of circumferential fibre shortening; mean VPW, mean normalised posterior wall velocity.

The average mean VPW during tocainide administration was 0·75 ± 0·05 s^{-1}. This increased to 0·87 ± 0·07 s^{-1} after atropine (P < 0·05), and then decreased to 0·71 ± 0·05 s^{-1} (P < 0·01 vs atropine, NS vs basal state) during phenylephrine infusion. Placebo values did not differ significantly from these values.

During the increase in heart rate after atropine, the mean left ventricular end-diastolic dimension in the placebo and tocainide groups decreased (both P < 0·05 vs basal state), and returned to basal state levels during phenylephrine infusion. The mean left ventricular end-systolic dimension did not change significantly in either group after atropine, but increased in both groups during phenylephrine infusion (P < 0·01 vs atropine, P < 0·05 vs basal state). In both the placebo and tocainide groups the mean left ventricular ejection times shortened after atropine (P < 0·01 vs basal state), and then returned towards basal state values during phenylephrine infusion (P < 0·05 vs atropine, NS vs basal state). Thus, for the placebo and tocainide groups alike, the increases in mean VCF values after atropine were largely the result of reductions in the left ventricular ejection time, and the decreases in mean VCF values during phenylephrine infusion were largely the result of increases in end-systolic dimensions and a return towards basal levels of left ventricular ejection times.

A typical response to an acute increase in heart rate and systemic arterial pressure is shown in the echocardiograms in the Fig. Though these recordings were made during tocainide therapy the response was the same whether the patient was taking tocainide or placebo.

Discussion

Little information is available concerning the effects of tocainide on left ventricular function. Duce *et al.* (1973), in a study of 6 conscious dogs, reported that oral tocainide in a dose of 25-200 mg/kg every 1 to 4 hours produced no alterations in systemic arterial or central venous pressure. However, Coltart *et al.* (1974) found moderate depression of cardiac function in 4 anaesthetised dogs given single oral tocainide doses of 120 mg/kg. Significant increases in left ventricular end-diastolic pressure and significant decreases in heart rate and left ventricular dP/dt were observed; plasma tocainide concentrations in both studies ranged from 15 to 30 μg/ml.

There are 5 previous reports of preliminary data concerning the use of tocainide as an antiarrhythmic agent in humans and in no study was cardiac depression observed (McDevitt *et al.*, 1976; Winkle *et al.*, 1976; Woosley *et al.*, 1977; Ryan *et al.*, 1978; Winkle *et al.*, 1978). However, the doses of tocainide employed were, per kg body weight, less than one-tenth the dose used by Coltart *et al.* (1974) in their animal study. Further, in none of these studies was the response to any controlled stress, such as acute increases in systemic arterial pressure, evaluated. In the present study the mean plasma drug concentration in the tocainide group at the time of the echocardiographic studies was 5·3 μg/ml, the range being from 2·0 to 7·3 μg/ml.

Nine of 10 patients had levels within the lower limits of the usual therapeutic range (> 4 μg/ml). These therapeutic levels were the result of choosing a dose of 400 mg of tocainide every 8 hours. This dose level was selected as a safety precaution because at the outset of the study the potential for myocardial depression of tocainide was unknown.

When mean VCF and mean VPW values are used to compare the inotropic status of the myocardium in an individual on different occasions as was done in this study it is important that heart rates and blood pressures are matched (Hirshleifer *et al.*, 1975). In the basal state the mean heart rates were similar in the tocainide and placebo groups but the mean systemic systolic blood pressures were slightly higher in the tocainide group. Experimental studies (Ross *et al.*, 1966; Mahler *et al.*, 1975) and studies in humans (Hirshleifer *et al.*, 1975; Quinones *et al.*, 1975) have documented a reduction in the extent and velocity of myocardial shortening as resistance to ejection is increased. However, despite the increase in mean basal state systolic blood pressure during tocainide, no significant reduction in mean VCF or mean VPW occurred. After atropine the mean heart rates for the placebo and tocainide groups did not differ significantly from each other. However, just as in the basal state, the mean systolic arterial pressure was higher in the tocainide group than in the placebo group. Again no significant differences were found between the mean VCF and mean VPW values in both groups.

The effects of acute alterations in systemic arterial pressure on isovolumic and ejection phase indices of left ventricular performance have previously been studied in our laboratory (Mahler *et al.*, 1975). This same technique has also been used to study the effects of drugs on left ventricular function (Mahler *et al.*, 1974; Crawford *et al.*, 1975; Gorwit *et al.*, 1975; Crawford *et al.*, 1976). In both normal conscious dogs (Mahler *et al.*, 1974) and normal human subjects (Crawford *et al.*, 1976) oral digoxin had a protective effect on left ventricular performance during acute pressure loading. In these studies the positive inotropic effect of digoxin was more apparent during than before acute pressure loading. By contrast, using similar techniques, we have been able to show that beta-adrenergic blockade exerts a modest but definite depressant effect on left ventricular function (LeWinter *et al.*, 1978). Further, another antiarrhythmic agent, quinidine gluconate, can be shown to be a myocardial depressant during acute afterloading when sympathetic tone is suppressed by beta-adrenergic blockade (Engler *et al.*, 1978). Therefore, we reasoned that if tocainide is a myocardial depressant, a further reduction in left ventricular performance compared with placebo values should be demonstrable during acute pressure loading. However, no latent alteration in left ventricular performance due to tocainide was 'unmasked'—the average mean VCF and mean VPW values during phenylephrine infusion were similar whether the patients were receiving tocainide or placebo.

Thus, under the conditions of our study tocainide in a typical therapeutic dose of 400 mg each 8 hours had no myocardial depressant action. However, no patient had severely depressed left ventricular function in the basal state (partly because patients with coronary artery disease and congestive cardiomyopathy were specifically excluded). The effect of tocainide on ventricular function when severely depressed function is present at rest or when higher drug doses are used is, therefore, still unknown. Thus the effects of tocainide on cardiac performance resemble those of lignocaine, which in large doses in experimental animals produces myocardial depression (Austen and Moran, 1965; Nayler *et al.*, 1969; Asokan *et al.*, 1968) but in conventional doses in man is devoid of significant cardiovascular effects (Harrison *et al.*, 1963; Grossman *et al.*, 1969; Rahimtoola *et al.*, 1971). Tocainide, however, has a major advantage that lignocaine does not have: it can be administered orally.

In summary, tocainide is an oral antiarrhythmic agent with no evident myocardial depressant effect when typical therapeutic drug doses are used in patients without severe left ventricular dysfunction. If the reported efficacy of tocainide is further confirmed, and if no severe toxic problems result from chronic administration of the drug, then it ought to be a useful antiarrhythmic agent. In this short-term study no laboratory abnormalities occurred during tocainide administration, but further long-term testing is required to demonstrate that the drug has no adverse systemic effects.

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Observations on haemodynamic effects of mexiletine

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SUMMARY The haemodynamic effects of intravenous mexiletine have been studied in 16 patients with valvular heart disease without clinical evidence of heart failure.

A bolus injection of 150 mg administered to 6 of the 16 patients resulted in a mean plasma concentration above the therapeutic range for at least 5 minutes after the drug was given. A small but significant rise in the mean pulmonary artery pressure occurred.

In 10 patients, the effects of intravenous mexiletine were compared with those of intravenous saline in a double blind trial. No significant difference was found in the haemodynamic effects, though both saline and mexiletine produced a small rise in the mean pulmonary artery pressure.

Mexiletine when administered to patients without heart failure in doses known to be clinically effective did not have important adverse haemodynamic effects.

Mexiletine, a relatively new antiarrhythmic drug, when given intravenously controls ventricular arrhythmias (Campbell *et al.*, 1977). Adverse haemodynamic effects were not observed when doses of from 50 to 140 mg were injected intravenously (Banim *et al.*, 1977; Pozenel, 1977). These doses are smaller than those used in clinical practice (Campbell *et al.*, 1977; Prescott, 1977). Preliminary studies from our laboratory showed a statistically significant fall in cardiac index and a rise in systemic vascular resistance in patients receiving 100 mg mexiletine intravenously (Campbell, 1976).

The investigation reported here was designed to clarify the haemodynamic effects of mexiletine given in bolus injections which are clinically effective.

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Patients and methods

The studies were performed in 16 patients undergoing cardiac catheterisation. Five patients had mitral valve disease, 2 had aortic valve disease, and 9 had disease of both valves. Two patients had grade 1 and 14 grade 2 disability (New York Heart Association classification) (Table 1). None had clinical evidence of heart failure. Thirteen were on maintenance digoxin therapy.

The procedure was explained and the patients' consent obtained. All were studied fasting and had received 50 mg pethidine and 5 mg droperidol by intramuscular injection at least 1½ hours before the investigation. The local anaesthetic was lignocaine, injected subcutaneously in a dose of 200 to 400 mg. The mean plasma concentration of lignocaine was 1·4 μg/ml (range 0·44 to 2·9 μg/ml).

Table 1 *Details of patients*

		Patients	*Age (y) (mean ± SEM)*	*Sex*		*Weight (kg) (mean ± SEM)*	*Functional class**		*Rhythm*		*No. receiving digoxin*
				M	*F*		*I*	*II*	*SR*	*AF*	
	150 mg Mexiletine	6	45·0 ±5·1	3	3	67·0 ±5·8	2	4	3	3	3
Double blind comparison	2·75 mg/kg Mexiletine	5	44·0 ±2·8	3	2	69·0 ±7·7	0	5	2	3	5
	Saline	5	44·0 ±5·4	3	2	61·0 ±4·6	0	5	1	4	5

SEM, standard error of mean; SR, sinus rhythm; AF, atrial fibrillation; *New York Heart Association classification.

The study was carried out in 2 parts. Six patients received 150 mg by intravenous injection and 10 were studied in a randomised double blind controlled comparison of the effects of mexiletine and saline (Table 1). In the 6 patients who were to receive 150 mg, right heart catheterisation was performed, using a double-lumen Cournand catheter inserted into a median cubital vein. The right atrial pressure was measured. The catheter was then advanced to the pulmonary wedge position. Simultaneous recordings of the pulmonary artery and pulmonary wedge pressures were obtained.

In the 10 patients in the double blind trial, the right heart was catheterised by a double-lumen flow directed balloon catheter. Positioning of the catheter allowed recording of the pulmonary arterial or pulmonary arterial occluded pressure simultaneously with the right atrial pressure. The pulmonary arterial occluded pressure was assumed to be identical to the pulmonary wedge pressure.

In all 16 patients, a number 7 Gensini catheter was introduced into a femoral artery and passed retrogradely into the left ventricular cavity. A 15 cm 'teflon' catheter was inserted into the other femoral artery. The electrocardiogram and all pressures were recorded on a direct writing 8-channel Mingograf 81 recorder. This machine was equipped with an ink jet recorder and had a linear frequency response from 0 to 500 Hz. The sternal angle was taken as the zero reference for all pressure measurements.

Tracings were obtained of the electrocardiogram and the left ventricular, pulmonary arterial, pulmonary wedge, or pulmonary arterial occluded and femoral arterial pressures at a paper speed of 25 mm/second. When the balloon catheter was used, the right atrial and pulmonary arterial pressures were measured simultaneously. In all studies immediately following the pressure recordings, the cardiac output was determined by the dye dilution method, using indocyanine green. The dye was injected into the pulmonary artery or right atrium and blood withdrawn through the femoral arterial catheter using a constant rate withdrawal pump. Changes in dye concentration were detected by a Gilford densitometer and displayed on a Texas instruments recorder.

The left ventricular end-diastolic pressure (LVEDP) was taken as the pressure immediately before the rapid rise caused by ventricular contraction. The mean right atrial and pulmonary wedge pressures were estimated from their tracings. Pressure determinations were made by analysis of 6 or more beats.

The systemic and pulmonary vascular resistances (SVR and PVR) were calculated: SVR = (mean femoral arterial pressure − mean right atrial pressure) ÷ CO; PVR = (mean pulmonary arterial pressure − mean pulmonary wedge pressure) ÷ CO. Stroke work index (SWI) was derived from the formula $\text{SWI} = (\text{LVMSP} - \text{LVEDP}) \times \frac{\text{Cardiac index}}{\text{Heart rate}} \times 0{\cdot}0136$ g m/beat per m^2 (Grossman, 1974) (LVMSP = the left ventricular mean systolic pressure = 0·9 × peak left ventricular systolic pressure (Russell *et al.*, 1970)).

In all studies, control measurements were made approximately 5 and 2 minutes before the administration of the drug. The 150 mg injection of mexiletine was given at a rate of 40 mg/minute. Recordings were repeated 2, 5, 10, 15, and 20 minutes after the completion of the injection. Blood samples were withdrawn after 2, 5, and 20 minutes for determination of the plasma concentration of mexiletine (Kelly, 1977).

In the randomised double blind controlled study, 5 patients received mexiletine in a dose of 2·75 mg/kg body weight. Five patients received an intravenous injection of similar volumes of normal saline. The drug or saline was infused over 2·5 minutes. Patients in the 2 groups were matched for age, sex, and heart size determined from the chest *x*-ray film. Pressure recordings and determination of cardiac output were made 2, 5, and 10 minutes after the completion of the injections. The results were calculated without knowledge of whether drug or saline had been given.

Statistical comparisons within groups of patients were made using Student's t test for paired differences. The statistical differences between mean values were determined with Student's unpaired t test.

Results

Table 2 shows the results after the administration of 150 mg mexiletine to 6 patients. Apart from a small rise in the mean pulmonary artery pressure, statistically significant changes did not occur.

Two minutes after completion of the injection, the mean plasma concentration of mexiletine was 3·9 ± 1·7 (SEM) μg/ml. Three minutes later, the mean value had fallen to 2·3 ± 1·2 (SEM) μg/ml. Twenty minutes after the injection, the mean concentration had fallen to 0·4 ± 0·1 (SEM) μg/ml.

The results of the randomised trial are shown in Table 3. Five patients received mexiletine in a dose of 2·75 mg/kg and, in these patients, the only statistically significant change was an increase in the mean pulmonary artery pressure. It rose from a mean value of 16 mmHg to 19 mmHg 2 minutes after the injection was given.

Table 2 *Haemodynamic effects of intravenous injection of 150 mg mexiletine in 6 patients*

		Control	*Minutes after injection*				
			2	*5*	*10*	*15*	*20*
Heart rate (beats/min)	Mean	69	71	71	70·5	70	69
	± SEM	3·7	5·9	5·6	6·0	5·5	4·9
Mean pulmonary artery pressure (mmHg)	Mean	13	13	15*	15	14†	13
	± SEM	1·9	1·9	2·4	2·6	1·8	1·4
Mean femoral artery pressure (mmHg)	Mean	74	72	75	74	75	75
	± SEM	3·8	3·5	5·1	4·0	3·9	4·2
Left ventricular end-diastolic pressure (mmHg)	Mean	6	6·5	7	5	4	6
	± SEM	0·7	0·8	1·4	0·7	0·3	0·9
Cardiac index (l/min per m^2)	Mean	2·3	2·1	2·3	2·2	2·4	2·3
	± SEM	0·20	0·37	0·37	0·39	0·41	0·41
Stroke work index (g m/beat per m^2)	Mean	45	40	44	43	51	47
	± SEM	5·7	7·7	8·1	8·4	12·3	9·1
Pulmonary vascular resistance (dynes s cm^{-5})	Mean	140	140	190	230	160	160
	± SEM	22	27	48	82	38	31
Systemic vascular resistance (dynes s cm^{-5})	Mean	1570	1850	1710	1810	1720	1770
	± SEM	160	333	294	333	347	287

*P < 0·02 } comparisons made with control values; SEM, standard error of mean.
†P < 0·01 }

Saline was given to 5 patients (Table 3). Five minutes after the injection, a mean increase in the mean pulmonary arterial pressure was observed. Five and 10 minutes after the saline injection, the mean femoral artery pressure increased by 4 mmHg. These changes were statistically significant. When the results obtained after 2, 5, and 10 minutes were combined, there were significant increases in the

Table 3 *Haemodynamic effects of mexiletine and saline*

		Mexiletine (5 patients)					*Saline (5 patients)*				
		Control	*Minutes after injection*			*Total*	*Control*	*Minutes after injection*			*Total*
			2	*5*	*10*			*2*	*5*	*10*	
Heart rate (beats/min)	Mean	62	66	64	64	64	68	69	69	70	69
	± SEM	4·8	4·3	4·3	3·3	3·8	9·1	8·9	8·8	9·6	9·1
Mean pulmonary artery pressure (mmHg)	Mean	16	19*	18	19	19	19	20	21*	19	20
	± SEM	2·7	3·0	2·9	3·4	3·0	3·0	3·3	3·3	2·7	3·1
Mean femoral artery pressure (mmHg)	Mean	77	79	72	77	76	68	69	72*	72†	71*
	± SEM	5·7	6·2	2·5	3·5	2·9	7·8	7·7	8·5	7·9	8·0
Left ventricular peak systolic pressure (mmHg)	Mean	109	106	105	101	104	98	102	100	99	100†
	± SEM	10·8	7·5	7·6	5·0	6·0	9·7	9·5	11·7	7·9	9·6
Left ventricular end-diastolic pressure (mmHg)	Mean	6	8	8	5	7	6	6	6	5	6
	± SEM	2·0	2·4	2·2	2·0	2·2	1·7	2·1	2·1	2·7	2·25
Cardiac index (l/min per m^2)	Mean	2·3	2·4	(2·2)	2·5	2·4	2·0	2·0	2·1	2·1	2·1
	± SEM	0·35	0·92	(0·37)	0·25	0·30	0·18	0·22	0·21	0·26	0·22
Stroke work index (g m/beat per m^2)	Mean	45	43	(44)	46	44	35	36	36	37	36
	± SEM	5·5	6·5	(6·0)	5·0	5·0	5·4	6·5	5·5	6·9	6·2
Pulmonary vascular resistance (dynes s cm^{-5})	Mean	190	200	(170)	180	190	210	180	180	180	170
	± SEM	57	51	(57)	43	48	40	40	46	28	34
Systemic vascular resistance (dynes s cm^{-5})	Mean	1660	1570	(1470)	1400	1490	1630	1640	1650	1680	1660
	± SEM	264	235	(218)	157	174	267	220	285	269	250

*P < 0·05 } comparisons made with control values.
†P < 0·01 }
Figures in parentheses are the values for 4 patients. Total refers to the combination of all results in each patient.

mean femoral artery and in the left ventricular peak systolic pressures.

When the results in the mexiletine group were compared with those in the patients who received saline, the mean changes in the measured and derived variables showed no statistically significant differences.

Discussion

The work of Singh and Vaughan Williams (1972) showed that mexiletine reduced the maximum amplitude of contraction of isolated rabbit atria. The effect occurred when the drug was present in the protein-free perfusate in a concentration of 3 μg/ml. Shaw (1977) used ball valve travel time in patients with a Starr-Edwards aortic prosthesis as an index of myocardial contractility. Travel time was significantly prolonged after 50 mg and 100 mg injections of mexiletine intravenously. The changes produced were similar to those observed with comparable doses of lignocaine. Saunamäki (1975) observed impairment of myocardial function in 3 of 6 patients with ischaemic heart disease who were given the drug by intravenous infusion. He gave 10 mg/minute for 10 minutes followed by a 6·5 mg/minute infusion for up to 12 minutes. The mean plasma concentration of mexiletine was > 1 μg/ml during the period of study. This is within the therapeutic range (Campbell *et al.*, 1978). The resting pulmonary wedge pressures of the 3 patients whose myocardial function deteriorated were 13 mmHg or higher and all had a current or past history of heart failure. We have previously reported the effects of mexiletine when systolic time intervals were used as an index of myocardial function (Campbell *et al.*, 1977). The ratio of the pre-ejection period to the left ventricular ejection time increased after the injection of 200 mg mexiletine in 6 patients with ischaemic heart disease. The change was most pronounced in 1 patient who had had congestive heart failure.

Banim *et al.* (1977) investigated the effects of mexiletine in patients with ischaemic heart disease whose mean left ventricular filling pressure at rest was 15·2 mmHg. No significant haemodynamic changes were observed when doses of 1·5 mg/kg (105 to 140 mg) were injected intravenously. Pozenel (1977) gave single injections of 50 or 100 mg and followed these by intravenous infusions of up to 500 mg within 50 minutes. No haemodynamic changes occurred.

The results of the present study are in keeping with the findings of Banim *et al.* (1977) and Pozenel (1977). We used larger doses and found that the only statistically significant change was a small rise in the mean pulmonary arterial pressure. A similar small rise was also observed in the patients who received saline. The doses of mexiletine which we used—150 mg and 2·75 mg/kg—are known to be effective in the control of ventricular arrhythmias (Campbell *et al.*, 1977; Prescott, 1977). The injection of 150 mg produced mean plasma concentrations of mexiletine above 2 μg/ml for at least 5 minutes. This level has been proposed as the upper limit of the therapeutic range of the drug (Campbell *et al.*, 1978). It is of interest that though lignocaine given for local anaesthesia resulted in a mean plasma concentration of 1·4 μg/ml no adverse interaction with mexiletine was observed.

Why some workers have shown negative inotropic effects whereas others have not may be explained by differences in the doses given or by the clinical status of the patients. A negative inotropic effect might be expected to occur more readily in those with poor left ventricular function. The intravenous injection of 200 mg mexiletine (Campbell *et al.*, 1977) or the administration of doses sufficient to raise the plasma concentration to adequate levels (Saunamäki, 1975) impaired cardiac performance, particularly when there was evidence of cardiac decompensation. Doses of 100 mg or less caused no deterioration in haemodynamics when the mean left ventricular filling pressure was normal (Pozenel, 1977). In the present study, none of the patients had clinical evidence of heart failure and only 1 had a left ventricular end-diastolic pressure above 13 mmHg. Doses of 150 mg or 2·75 mg/kg did not affect cardiac performance.

It is concluded that the intravenous administration of mexiletine in clinically effective dosage produced no adverse haemodynamic effects in patients without clinical evidence of heart failure.

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Haemodynamic effects of sodium nitroprusside in 21 subjects with congestive heart failure[1]

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SUMMARY Twenty-one patients in severe congestive heart failure refractory to conventional medical management were treated with sodium nitroprusside on 22 occasions. On 14 occasions (responders) there was significant improvement in clinical and haemodynamic indices. On 8 occasions (non-responders) hypotension developed without haemodynamic improvement and nitroprusside treatment had to be abandoned. The initial mean arterial pressure and the capillary wedge pressure tended to be higher in the responders while the cardiac index tended to be higher in the non-responders. The systemic vascular resistance was higher in the responders than in the non-responders (2560 ± 160 vs 1800 ± 180 dynes s cm^{-5}, $P < 0 \cdot 001$). All of the responders had systemic vascular resistance greater than 1900 dynes s cm^{-5}, while only one of the non-responders had a systemic vascular resistance in this range. Thus, a variable response to vasodilator therapy for congestive cardiac failure is documented. The favourable response appears to be limited to patients with a high systemic vascular resistance.

Recent investigations have shown the effectiveness of vasodilator therapy in a number of clinical situations associated with severely impaired left ventricular function. Improvement has been shown in patients suffering from acute myocardial infarction with left ventricular failure (Franciosa *et al.*, 1972; Chatterjee *et al.*, 1973a), in those with severe mitral regurgitation (Chatterjee *et al.*, 1973b), and in the treatment of chronic congestive heart failure refractory to the usual forms of treatment (Majid *et al.*, 1971; Guiha *et al.*, 1974; Miller *et al.*, 1975).

The basis of this mode of treatment (Cohn, 1973a, b) is a reduction of impedance to left ventricular outflow by lowering the resistance of the arteriolar bed and increasing the compliance of the large arteries. There is, in addition, venous vasodilatation and a consequent increase in venous capacitance; a reduction in ventricular preload follows (Cohn *et al.*, 1972; Chatterjee *et al.*, 1973a; Miller *et al.*, 1975). The effects on the heart are a rise in ejection fraction as ventricular wall tension declines, and a decrease in left ventricular size with an increase in stroke volume. The increase in cardiac output offsets the decreased systemic vascular resistance thus helping to maintain blood pressure at or near control levels. Myocardial oxygen is reduced since nitroprusside does not increase ventricular contractility or heart rate when used in the recommended manner.

Sodium nitroprusside has been used for this purpose because of its rapid action and high potency. Tachyphylaxis has not been noted with its use (Palmer and Lasseter, 1975). Certain safeguards are essential for its safe use, however, including measuring ventricular filling pressures, cardiac output, and systemic arterial pressure before and during its administration.

Despite its reported beneficial effects, the administration of sodium nitroprusside to patients in severe congestive failure in our coronary care unit (CCU) has, on occasion, been noted to result in a deterioration clinically as well as haemodynamically. Such deterioration occurs either acutely or even after a transient period of improvement. In this report we wish to document the varying haemodynamic responses in 21 patients who were treated with sodium nitroprusside on 22 occasions, in an attempt to provide guidelines for its safe use in the management of severe and often refractory congestive heart failure.

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Subjects and methods

Twenty-one patients, aged 16 to 76 years (mean 50 years) of whom 17 were men and 4 women, were studied. All were in severe congestive heart failure (NYHA Class IV) which had proved refractory to maximal conventional treatment using digoxin, diuretics, bedrest, and sodium restriction.

Symptoms of failure had been present for 1 to 6 years necessitating many admissions to hospital for all these patients. The causes of the congestive cardiac failure were: coronary heart disease in 7 (documented by cardiac catheterisation in 6); congestive cardiomyopathy in 14 (documented by cardiac catheterisation in 8).

After informed consent had been obtained the patients were studied in the CCU. A Swan-Ganz balloon-flotation catheter and a 'teflon' arterial catheter were inserted under local anaesthesia into the brachial vein and artery, respectively (Resnekov and Lipp, 1971). The pulmonary capillary wedge pressure or the pulmonary artery diastolic pressure were used to approximate the left ventricular filling pressure (Falicov and Resnekov, 1970). Cardiac output was measured in duplicate using the dye dilution technique. Systemic vascular resistance was calculated as:

$$\frac{\text{MAP-RAP}}{\text{CO}} \times 80 \text{ dynes s cm}^{-5} \text{ and}$$

left ventricular stroke work index as:

$$\text{SVI} \times (\text{MAP-LVFP}) \times 0{\cdot}0144 \text{ g m per m}^2$$

where MAP is mean arterial pressure, RAP is right atrial pressure (both in mmHg), SVI is the stroke volume in ml per m^2 body surface area, and CO is the cardiac output in l/min.

After control measurements had been made, sodium nitroprusside was administered using an infusion pump starting with a dose of 0·5 μg/kg per min and increasing until a fall in blood pressure occurred. Cardiac output and pressures were measured again and the dose of nitroprusside titrated to maximise cardiac output without unduly reducing mean arterial pressure. The therapeutic trial was stopped if the systemic arterial pressure fell to 65 mmHg or less or in patients in whom the cardiac output could not be increased without causing significant arterial hypotension. Otherwise treatment with nitroprusside continued for 2 to 7 days.

Treatment measurements contained in this report reflect those after 24 hours of nitroprusside infusion, unless the trial was stopped earlier, in which case the values shown represent the highest dose tolerated before the infusion was stopped. For purposes of analysis, patients were regarded as 'non-responders' if the therapeutic trial was stopped because of hypotension. Patients were classified as 'responders' if an improvement in both clinical and haemodynamic indices was observed. When the patients left hospital, those classified as responders were prescribed regimens consisting of isosorbide dinitrate and, on occasion, hydralazine as well, in addition to continuing digoxin and diuretic therapy.

Results

Of the 21 patients studied, 13 showed a favourable clinical and haemodynamic response documented by an increased diuresis, decreased symptoms, lowering of the indirect left ventricular filling pressure associated with an enhanced stroke volume and cardiac index without tachycardia or hypotension. This was sustained for at least 24 hours. Seven patients, however, who failed to show any clinical or haemodynamic improvement were classified as non-responders. One patient (case 9) did respond favourably when studied first, but 18 months later when restudied failed to respond clinically or haemodynamically.

RESPONDERS

On 14 occasions there was a favourable response to the nitroprusside infusion, resembling that seen by several other observers (Guiha *et al.*, 1974; Miller *et al.*, 1975) (Fig. 1). Thus, nitroprusside reduced the systemic vascular resistance by 50 per cent or more (from 2560 ± 160 to 1070 ± 80 dynes s cm^{-5}, $P < 0{\cdot}001$) while stroke volume (29 ± 3 to 65 ± 6 ml, $P < 0{\cdot}001$), cardiac index (1·5 ± 0·1 to 3·0 ± 0·20 l/min per m^2, $P < 0{\cdot}001$), and stroke work index (14 ± 2 to 30 ± 3 g m per m^2, $P < 0{\cdot}001$) approximately doubled. Mean arterial blood pressure fell (from 98 ± 4 to 79 ± 3 mmHg, $P < 0{\cdot}001$), while the average heart rate declined insignificantly (from 94 ± 6 to 84 ± 5). The indirect left ventricular filling pressure also fell by almost one-half (from 36 ± 3 to 21 ± 1 mmHg, $P < 0{\cdot}001$) (Table A).

These haemodynamic changes were accompanied by evidence of clinical improvement in the cardiac failure and by an enhanced diuresis.

Follow-up of the patients which was maintained for 2 to 24 months after the study revealed that 4 deaths occurred during this time, 3 of which were directly attributed to their cardiac disease.

NON-RESPONDERS

Treatment with nitroprusside was discontinued on 8 occasions because an improvement in cardiac output could not be achieved without compromising the blood pressure. On 7 occasions, there was a transient period of improved cardiac output and lowered

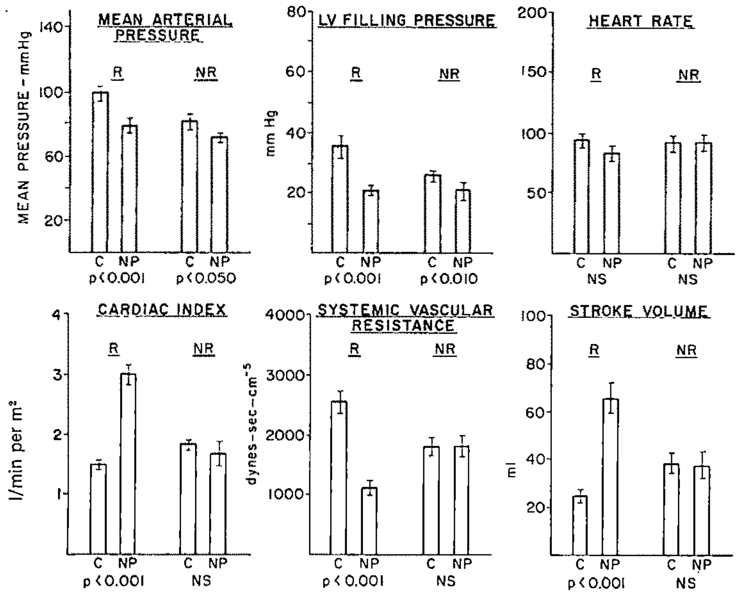

Fig. 1 *Haemodynamic values during control (C) and nitroprusside infusion (NP) measurements in responders (R) and non-responders (NR).*

able *Summary of haemodynamic data*

se no.	*Age (y)*	*Mean arterial pressure (mmHg)*		*Left ventricular filling pressure*† *(mmHg)*		*Cardiac output (l/min)*		*Cardiac index (l/min per m²)*		*Heart rate/min*		*Stroke volume (ml/stroke)*		*Systemic vascular resistance (dynes s cm⁻⁵)*		*Stroke work index (g m per m²)*	
		C	*NP*	*C*	*NP*	*C*	*NP*	*C*	*NP*	*C*	*NP*	*C*	*NP*	*C*	*NP*	*C*	*NP*
Responders																	
	44	110	80	45	20	2·7	7·3	1·4	3·6	118	125	23	56	2670	830	11	25
	65	120	105	32	16	3·9	5·3	2·0	2·7	80	68	49	79	2460	1580	32	53
	38	90	80	30	25	2·4	6·6	1·3	3·6	96	96	25	69	2800	910	11	29
	50	120	90	60	25	2·4	4·5	1·3	2·4	124	88	19	51	3400	1510	9	25
	56	85	80	40	20	2·5	6·3	1·4	3·4	63	68	40	93	2400	890	14	43
	45	117	97	20	20	3·2	8·2	1·5	3·8	101	84	31	101	2670	940	21	51
	60	93	70	30	20	3·1	4·6	2·1	3·1	90	78	29	59	2190	1130	18	31
	25	85	75	33	15	2·6	7·2	1·5	4·1	92	98	28	75	2480	730	12	36
$_1$*	55	73	65	40	20	2·3	4·0	1·2	2·2	132	80	17	50	1980	1090	4	18
	43	100	70	40	30	2·9	5·2	1·7	3·1	88	88	33	59	2060	920	16	20
	16	95	70	35	23	2·1	3·5	1·2	2·0	110	97	19	36	2860	1260	10	28
	40	90	80	35	30	2·8	5·0	1·6	2·8	90	84	31	60	2000	1000	10	22
	60	92	65	30	20	3·3	5·9	1·7	3·0	60	60	56	98	1930	680	15	27
	60	95	80	30	15	1·4	3·9	0·8	2·5	68	68	12	28	4000	1440	14	16
	Mean	98	79	36	21	2·7	5·5	1·5	3·0	94	84	29	65	2560	1070	14	30
	SEM	4	3	3	1	0·2	0·4	0·1	0·2	6	5	3	6	160	80	2	3
	P	<0·001		<0·001		<0·001		<0·001		NS		<0·001		<0·001		<0·001	
Non-responders																	
	35	75	72	25	20	4·4	3·8	2·0	1·8	108	108	41	33	1280	1510	14	11
	57	75	80	24	15	3·1	2·4	1·5	1·1	96	112	32	26	1680	1830	11	11
	27	95	70	30	25	2·3	1·8	1·5	1·1	120	96	19	20	2960	2700	11	8
	76	75	70	25	22	4·1	5·8	2·2	3·2	88	98	47	66	1460	870	19	29
	72	80	70	25	20	3·0	3·4	1·7	1·9	72	72	42	47	1840	1930	18	19
	25	95	75	30	30	4·7	3·8	2·4	1·9	90	88	50	43	1440	1360	23	17
	53	75	70	25	15	3·1	2·9	1·8	1·7	88	85	35	34	1780	1930	14	19
$_2$*	57	77	70	22	22	2·9	2·0	1·4	1·2	80	80	36	27	1900	2800	12	8
	Mean	81	72	26	21	3·5	3·2	1·8	1·7	93	92	38	37	1800	1800	15	15
	SEM	3	1	1	2	0·3	0·5	0·1	0·2	5	5	3	5	180	230	2	2
	P	<0·050		<0·010		NS		NS		NS		NS		NS		NS	

Case 9 was studied on two separate occasions separated by an 18-month interval.
Indirect measurement. C, control; NP, nitroprusside.

systemic vascular resistance, but thereafter (usually within 16 hours) the mean arterial pressure fell to unacceptable levels. Six patients had a decrease in cardiac output. Two patients (cases 18 and 19) experienced a modest increase in cardiac output which was insufficient to maintain the mean arterial pressure in the face of the decreased peripheral resistance. As a result, the group as a whole demonstrated no change in cardiac output, systemic vascular resistance, stroke volume, or stroke work index, despite a drop in arterial pressure from 81 ± 3 to 72 ± 1 ($P < 0\cdot05$) (Table B). The capillary wedge pressure also fell, from an average of 26 ± 1 to 21 ± 2 ($P < 0\cdot01$). Several of these patients subsequently required dopamine to maintain the blood pressure despite stopping nitroprusside. No patients experienced any untoward symptoms during the nitroprusside infusion (and no myocardial infarctions were documented).

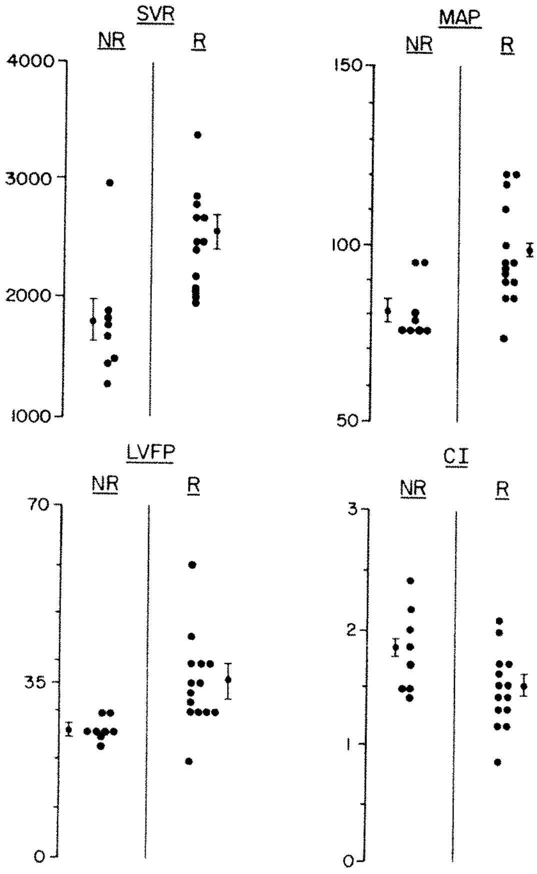

Fig. 2 *Control haemodynamic values in non-responders (NR) and responders (R). SVR, systemic vascular resistance (dynes s cm^{-5}); MAP, mean arterial pressure (mmHg); LVFP, indirect left ventricular filling pressure (mmHg); CI, cardiac index (l/min per m^2).*

Six of the non-responders died between 2 weeks and 2 months after study. All the deaths were attributed to cardiac failure and its complications.

Discussion

On the basis of the data obtained from the 21 patients studied it is recommended that when treatment with nitroprusside is being considered for the management of severe cardiac failure, particular attention should be paid not only to an assessment of left ventricular filling pressure but also to the level of the systemic vascular resistance.

Comparison of the control data for the two groups showed that they could not be distinguished on the basis of age, aetiology of failure, the physical signs, or by renal function. However, the haemodynamic data showed (see Fig. 2) that mean arterial pressure tended to be higher for the responders than for the non-responders (98 ± 4 vs 81 ± 3, $P < 0\cdot005$) as did left ventricular filling pressure (36 ± 3 vs 26 ± 1, $P < 0\cdot005$). Cardiac index tended to be higher for the non-responders ($1\cdot5 \pm 0\cdot1$ vs $1\cdot8 \pm 0\cdot1$, $P < 0\cdot005$), while stroke volume and stroke work index were not significantly different between the two groups. There was, however, an overlap between the two groups making it difficult to predict the response in any individual patient. The systemic resistance was higher in the responders than in the non-responders (2560 ± 160 vs 1800 ± 180, $P < 0\cdot01$) and, while all responders had a systemic vascular resistance greater than 1900 dynes s cm^{-5}, only one non-responder had one in this range. Fisher's exact test (Brownlee, 1960) revealed the difference in systemic vascular resistance to be a significant prognostic indicator ($P < 0\cdot001$).

Reports to date have emphasised the benefits of vasodilator therapy in congestive failure. The results obtained in this study suggest that there exists a group of patients in whom vasodilator therapy is not beneficial. An adverse response to nitroprusside has been noted to be associated with normal or low ventricular filling pressures in both acute myocardial infarction (Chatterjee *et al.*, 1973a) and in chronic ischaemic heart disease (Miller *et al.*, 1975). In this study the observations that the indirect left ventricular filling pressure tended to be higher in the group that responded to treatment supports the importance of assessing left ventricular filling pressure before and during treatment with nitroprusside. In none of our patients, however, did nitroprusside reduce the raised indirect left ventricular filling pressure to the normal range.

The importance of knowing the systemic vascular resistance before using nitroprusside is shown by the fact that it was, in fact, the single most useful index for predicting the response. The raised systemic vascular resistance in those who respond favourably appears to be an inappropriate compensatory mechanism, the effect of which is to reduce cardiac output by increasing the afterload and thus opposing ventricular ejection. In contrast, however, in those who failed to respond to sodium nitroprusside, the systemic vascular resistance was closer to the normal range and attempts to reduce it were not associated with any improvement in the status of the patients. Thus, in those who do not respond to nitroprusside left ventricular dysfunction appears to be less dependent on afterload.

As shown by the haemodynamic measurements in the 21 patients congestive cardiac failure represents a heterogeneous syndrome. Ventricular filling pressure and systemic resistance vary greatly between patients and in the extent to which they compromise or support left ventricular function. Vasodilator therapy appears to be of most value in those in whom high afterload plays an important role in left ventricular dysfunction, and in whom ventricular filling pressures greatly exceed normal values.

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Haemodynamic adaptation at rest and during exercise to long-term antihypertensive treatment with combined alpha- and beta-adrenoreceptor blockade by labetalol

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SUMMARY The effects on systemic and pulmonary haemodynamics of treatment with the alpha- and beta-adrenoceptor blocker labetalol for 20 months were studied in 9 hypertensive men aged 49 to 57 years, at rest in the supine and upright position and during exercise in the sitting position at 62 and 124 Watts. Pressures were recorded by means of catheters inserted percutaneously into the pulmonary and brachial artery, and cardiac output was determined by the Fick method.

Systemic systolic, diastolic, and mean pressures were considerably reduced by labetalol under all conditions. Pulmonary mean pressure was slightly higher during exercise, and left ventricular (pulmonary artery) diastolic pressure was virtually unchanged.

Systemic blood pressure was lowered by reduction of systemic vascular resistance alone. Though heart rate was significantly reduced under all conditions, cardiac output was unchanged because of a considerable rise in stroke volume which entirely counterbalanced the reduction in pulse rate. Compared with the haemodynamic pattern induced by intravenous labetalol, prolonged treatment resulted in a greater increase in stroke volume and a further decrease of heart rate, particularly at rest. Systemic vascular resistance showed a further tendency towards lower values. Postural hypotension which occurred frequently after intravenous labetalol was not observed after long-term treatment. Plasma renin activity and arterial lactate were consistently reduced. No serious side-effects were observed, nor were there any significant changes in haematological and biochemical variables.

Treatment of hypertension by combined alpha- and beta-receptor blockade using labetalol offers significant haemodynamic advantages compared with treatment by beta-receptor blockade alone.

Animal and human studies have shown that hypertension rapidly induces structural changes in the precapillary resistance vessels, including reduced internal vessel radius, increased wall to lumen ratio, and a consequent hyperactivity of these vessels with exaggerated luminal reductions for a given smooth muscle activation (Folkow, 1975). Recent studies also suggest that these structural changes may be reversible under certain conditions, both in the experimental animal (Weiss *et al.*, 1974) and in man (Sivertsson, 1977). Constriction of the peripheral resistance vessels is mediated through α-adrenoreceptors. Thus blockade of these receptors appears on theoretical grounds to be the most logical and efficient way to lower precapillary resistance and to damp the functional excitatory influences which, once the structural changes are established, enhance increases in the vascular pressure load and in turn serve to intensify the structural adaptation.

Agents with α-adrenoreceptor blocking properties such as phentolamine (Majid *et al.*, 1974) and labetalol (Koch, 1976b) have consistently been shown to reduce systemic vascular resistance and thereby blood pressure in man, at least in the acute experiment. As labetalol combines alpha-receptor with beta-receptor blocking properties it has an essential advantage over phentolamine and other peripheral vasodilators such as hydralazine and prazosin (Zacest, 1975), in that it counteracts the

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baroreceptor reflex increase of heart rate and cardiac output elicited by the pressure decrease.

Labetalol has been shown to have a considerable antihypertensive action (Richard and Turner, 1976; Brogden *et al.*, 1978). In the acute experiment it reduces blood pressure, at rest and during exercise, by lowering both the systemic vascular resistance and cardiac output but not stroke volume (Koch, 1976b, 1977). This pattern of haemodynamic effect distinguishes labetalol from most if not all other single antihypertensive drugs and offers a particularly attractive basis for treating hypertension from the physiological point of view.

Our knowledge of the haemodynamic effects of labetalol relates at present mainly to the acute intravenous administration of the drug. However it is well established that with many agents interfering with cardiovascular regulation, including antihypertensive drugs, the acute haemodynamic effects are attenuated or modified after prolonged treatment (Koch, 1976a). The purpose of the present study was, therefore, to define the long-term effects of oral labetalol with respect to circulatory dynamics. The haemodynamic effects on the systemic and pulmonary circulations in patients with essential hypertension have been investigated during rest in both supine and upright positions and during exercise.

Patients

Of the 13 patients who had participated in the initial investigation (Koch, 1977a), 9 men aged 49 to 57 years were restudied after an average of 20 months (range 16 to 24 months) treatment with oral labetalol as the sole antihypertensive agent in doses ranging from 600 to 2400 mg daily. Doses had to be repeatedly increased during the initial 6 months of oral treatment in order to maintain a similar blood pressure reduction as that obtained after the intravenous administration of labetalol; subsequently the dosage could be kept unchanged or slightly reduced.

The clinical evaluation indicated that all patients had essential hypertension; plasma volume, blood counts, serum electrolytes, serum creatinine, liver and renal function tests were normal and virtually unchanged during the entire period of observation. In particular, there was no case of positive antinuclear factor during a total observation time exceeding 3 years. Fundoscopic examination before and after the 20-month period did not reveal any significant alteration: one patient had no abnormalities at all, the remainder had non-exudative grade 1 to 2 hypertensive changes. None had evidence of ischaemic heart disease as evaluated by repeated exercise electrocardiograms (maximal work load ranging between 150 and 200 Watts) or of significant cardiac enlargement. Some relevant patient data including blood volume, heart volume, total amount of haemoglobin, and plasma renin activity before, and their changes after, the 20-month period, are given in Table 1.

Table 1 *Means and standard deviations (SD) of some anthropometric data and of plasma renin activity (PRA) before and mean ($\bar{D}$) and percentage ($\bar{D}$%) changes after 20 months of antihypertensive treatment*

	Mean	*SD*	$\bar{D}$	$\bar{D}$%
Age (y)	53·8	2·6	1·8	3·2
Weight (kg)	83·4	8·1	− 1·5	− 1·8
Height (cm)	176·3	6·0	0	0
Blood volume (l)	6·49	1·24	− 0·45	− 6·9
Total Hb (g)	859	202	− 92	− 10·7
PRA (ng/ml per h)	2·10	1·96	− 1·3**	− 63·0**

** $P < 0{\cdot}01$.

Methods

Haemodynamics were restudied after the 20-month period of oral treatment in precisely the same way and under conditions identical to the initial haemodynamic investigation. The haemodynamic measurements were made both in the supine and the upright positions and during steady state exercise at two different work loads (W_1: 62 ± 8, mean ± standard deviation, range 50 to 75 W; W_2: 124 ± 16, range 100 to 150 W) in the sitting position on a bicycle ergometer.

Both the orthostatic test and exercise at each work load lasted for 6 minutes. Systemic and pulmonary arterial pressures were directly recorded through polyvinyl catheters percutaneously introduced into the left brachial artery and the main pulmonary artery. Cardiac output was determined according to the Fick principle. Details concerning the general investigation procedure, analyses, calculations, including the reproducibility of the methods used and the statistical evaluation, are given elsewhere (Koch, 1976a, 1977).

Results

HAEMODYNAMICS AFTER LONG-TERM ORAL TREATMENT

Mean values and standard deviations of some relevant haemodynamic indices as measured before, as well as the changes observed after treatment, are given in Tables 2 and 3 and in Fig. 1.

Table 2 *Means and standard deviations (SD) of blood pressures and vascular resistances before and their mean changes ($\bar{D}$) after 20 months of antihypertensive treatment at rest in supine (R) and upright (O) position and during exercise at two different work loads*

		Mean	*SD*	$\bar{D}$
Brachial artery				
Systolic pressure (mmHg)	R	167	24	−18*
	O	174	31	−27**
	W_1	198	31	−42**
	W_2	235	23	−57**
Diastolic pressure (mmHg)	R	98	13	−17**
	O	104	17	−19**
	W_1	100	16	−20*
	W_2	111	17	−26**
Mean pressure (mmHg)	R	124	15	−18**
	O	133	22	−23**
	W_1	143	18	−32**
	W_2	162	20	−37**
Pulmonary artery				
Systolic pressure (mmHg)	R	22	6	3
	O	19	6	− 2
	W_1	30	6	5*
	W_2	36	9	5
Diastolic pressure (mmHg)	R	4	3	4
	O	3	3	1
	W_1	7	2	5
	W_2	11	4	4
Mean pressure (mmHg)	R	11	4	3
	O	8	4	1
	W_1	16	5	6*
	W_2	21	7	8*
Systemic vascular resistance index	R	48·8	12·1	− 9·3*
	O	57·4	14·7	−13·6*
	W_2	25·7	5·8	− 4·4*
Pulmonary vascular resistance index	R	3·0	1·3	− 0·7
	O	2·4	1·2	0
	W_2	1·6	0·6	0·8*

* $P < 0{\cdot}05$;
** $P < 0{\cdot}01$.
W_1 = 62 Watts;
W_2 = 124 Watts.

The pretreatment average systemic blood pressure was 167/98 (mean 124) mmHg at rest in the supine and 174/104 (mean 133) mmHg in the upright position. It rose to 235/111 (mean 162) mmHg during exercise (W_2). Treatment with oral labetalol resulted in a significant reduction (by 11 to 25%) under all conditions, the effect being most pronounced during exercise. At rest, both in the supine and upright posture, mean and diastolic pressures were affected more than systolic pressures.

Blood pressures in the pulmonary circulation were within normal limits both before and after treatment. Except for upright conditions there was a general tendency towards slightly higher values after treatment, in particular as regards systolic ($P < 0{\cdot}05$, W_1) and mean pressures ($P < 0{\cdot}05$, W_1 and W_2) during exercise. However, the absolute changes in pressure were minimal.

Heart rates were significantly reduced during all conditions (by 13 beats in the supine position and 28 beats during W_2); oxygen uptake ($\dot{V}O_2$) and ventilation ($\dot{V}E$) were unaffected.

Because of a significant increase in stroke volume which fully counterbalanced the reduction in heart rate, cardiac output was virtually unchanged. The arteriovenous oxygen difference was slightly reduced in the supine position only.

Pretreatment systemic vascular resistances were greatly increased at rest, both in the supine and especially in the upright positions. They were considerably reduced during all conditions after treatment (by 19 to 27%). Pulmonary vascular resistances were low before and after treament, and did not show any consistent change during the 20-month period.

Plasma renin activity (Table 1) and arterial blood lactate levels were significantly reduced (by 35 to 65%) under all conditions.

Table 3 *Means and standard deviations (SD) of some circulatory and respiratory variables before and their mean changes ($\bar{D}$) after 20 months of antihypertensive treatment at rest in supine (R) and upright (O) position, and during exercise at two different work loads*

		Mean	*SD*	$\bar{D}$
Heart rate	R	72	8	− 13***
	O	81	14	− 18**
	W_2	139	20	− 28**
Ventilation $\dot{V}_E$ (l/min BTPS)	R	11·6	4·6	− 1·4
	O	15·5	5·0	− 2·6
	W_2	56·6	10·5	− 2·3
Oxygen uptake, $\dot{V}o_2$ (l/min STPD)	R	262	42	− 3
	O	351	66	− 43
	W_2	1805	184	−115
AVo₂ difference (ml/l)	R	51·0	11	− 3
	O	76·0	12	− 13**
	W_2	139·6	12	− 2
Cardiac output (l/min)	R	5·42	1·57	0·13
	O	4·81	1·21	0·21
	W_2	13·06	1·87	− 0·71
Stroke volume (ml)	R	75	20	22*
	O	65	21	16
	W_2	94	11	17
Lactate (mmol/l)	R	0·97	0·39	− 0·57**
	O	1·01	0·47	− 0·66**
	W_2	3·93	0·71	− 1·39***
	4′ after work	4·39	1·05	− 1·56***

W_1 = 62 W; W_2 = 124 W.
*$P < 0·05$;
**$P < 0·01$;
***$P < 0·001$.

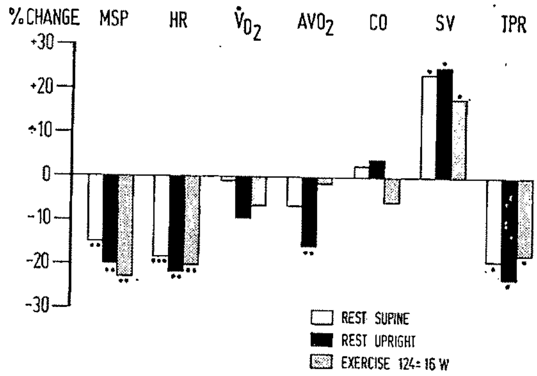

Fig. 1 *Percentage changes from pretreatment values of some haemodynamic variables after 20 months of antihypertensive treatment. MSP, mean systemic blood pressure; HR, heart rate; $\dot{V}o_2$, oxygen uptake; AVo_2, arterio-mixed venous oxygen difference; CO, cardiac output; SV, stroke volume; TPR, total peripheral resistance. Asterisks denote level of statistical significance: * $P < 0·05$, * * $P < 0·01$, * * * $P < 0·001$.*

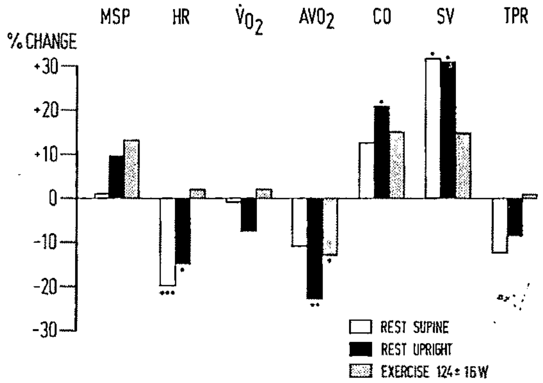

Fig. 2 *Percentage changes in some haemodynamic variables after 20 months of oral treatment compared with values measured after acute intravenous administration of 50 mg labetalol. Abbreviations and symbols as in Fig. 1.*

HAEMODYNAMICS AFTER LONG-TERM ORAL TREATMENT COMPARED WITH ACUTE INTRAVENOUS TREATMENT

Fig. 2 denotes the changes in the main haemodynamic indices that were observed after oral treatment compared with the haemodynamics as induced by acute intravenous administration of 50 mg labetalol (Koch, 1977a).

Mean systemic blood pressures were virtually unchanged at rest in the supine position; there was a weak yet statistically insignificant tendency towards slightly higher pressures in the upright position and during exercise. Heart rate showed a further decrease, at least during resting conditions, while stroke volume was significantly higher (23% in the upright position, $P < 0{\cdot}05$) resulting in slightly increased cardiac output. In accordance with the increased cardiac output the arteriovenous oxygen difference was significantly lower, particularly in the upright position. The systemic vascular resistance showed a further tendency towards lower values at rest.

Discussion

Treatment with oral labetalol for an average duration of 20 months resulted in considerably lower blood pressures under all conditions. Systemic mean pressures were reduced by 18 and 23 mmHg at rest in the supine and erect posture, and by 32 and 37 mmHg during exercise at loads W_1 (62 ± 8 W) and W_2 (124 ± 16 W corresponding to an oxygen uptake of approximately 1·8 l), respectively.

The mode of antihypertensive action was practically identical at rest, both in the supine and erect posture, and during exercise. Blood pressure was lowered by a reduction of peripheral vascular resistance alone; though heart rate was significantly lower under all conditions, cardiac output was virtually unchanged because of a considerable increase in stroke volume which entirely counterbalanced the reduction in pulse rate. It is particularly noteworthy that the increase in stroke volume which was consistently observed under all conditions was achieved without any significant rise in pulmonary artery diastolic pressure, that is in left ventricular filling pressure. Though the use of left ventricular filling pressure as a method of evaluating myocardial contractility is crude and insensitive, the absence of any significant pressure rise both at rest and particularly during exercise, in association with considerably increased stroke volumes, suggests that labetalol lacks significant negative inotropic effects.

A completely different pattern of haemodynamic adaptation is regularly seen with agents that exclusively block adrenergic beta-receptors. In the rare instances when left ventricular filling pressures were measured during long-term oral treatment with beta-blockers, left ventricular filling pressures were regularly found to be higher at corresponding exercise levels. This applies for oxprenolol and propranolol (Taylor *et al.*, 1970) as well as for the combination of oxprenolol and hydralazine (Koch, 1976a). Cardiac output was found to be consistently reduced, and the arteriovenous O_2 difference correspondingly increased, during both resting and exercise conditions, after long-term treatment with alprenolol, atenolol, metoprolol, and timolol, while the peripheral vascular resistance consistently showed a tendency towards slightly higher values (Lund-Johansen and Ohm, 1976). The same general pattern of haemodynamic adjustment was observed after a 13-month treatment with oxprenolol despite supplementary administration of the vasodilator hydralazine in a daily dose ranging between 150 and 225 mg during the last 6 months (Koch, 1976a). Data obtained during treatment with propanolol, though limited to resting conditions, suggest a similar haemodynamic response (Tarazi and Duston, 1972), even when combined with hydralazine (Trap-Jensen *et al.*, 1976a). A particular feature of Tarazi's study was the observation that systemic vascular resistance was greatly increased in the early stage of treatment, but approached pretreatment levels after a period of 20 months of treatment. Surprisingly enough, pindolol, a nonselective beta-receptor antagonist, has recently been reported to lack the cardiac output reducing effect on long-term treatment and to exert its antihypertensive action solely by reduction of the peripheral vascular resistance (Atterhög *et al.*, 1977). However, the mechanism behind this effect, unusual for a beta-receptor blocker, remains obscure.

The considerable reduction in total peripheral vascular resistance in association with unchanged cardiac output (Fig. 1) suggests that labetalol, because of its alpha-receptor antagonism, might lack the flow reducing effect exerted by propranolol in different vascular beds such as the splanchnic-hepatic circulation and the skeletal muscle (Trap-Jensen *et al.*, 1976b). The significant reduction in arterial blood lactate during and after exercise while on prolonged treatment (Table 3) might indicate a different action of labetalol with respect to microcirculation and/or metabolism, since lower lactate levels probably reflect a lesser degree of anaerobic metabolism in the working muscles. A decline of lactate was not seen after the acute administration of labetalol (Koch, 1977) and clonidine (Koch, 1971), or after long-term treatment with propranolol (Trap-Jensen *et al.*, 1976b) and with oxprenolol in combination with hydralazine (Koch, 1976a), that is conditions where cardiac output was consistently reduced. Recent studies on renal haemodynamics have also shown a reduction in renal vascular resistance after the administration of labetalol (Koch, 1978).

During the acute experiment, signs and symptoms of conspicuous postural hypotension were frequent (Koch, 1976b), but were not observed after long-term oral treatment. Neither did any of the patients complain of signs attributable to decreased orthostatic tolerance in daily life activities during a total observation period of 3 years. The acute effects of labetalol consist mainly in a negative chronotropic action via beta-receptors in the myocardium and in an alpha-receptor mediated dilatation of the resistance vessels inducing a reduction of cardiac output and predominantly of vascular resistance; but intravenous labetalol also results in lower pulmonary artery pressures and tends to decrease left ventricular filling pressures (Koch, 1977). These latter effects suggest that the acute administration of the drug also induces, particularly in the supine and upright position, a blood volume shift from the intrathoracic to the peripheral compartments of the low pressure capacitance system. This peripheral blood pooling is probably the result of a vasodilatory effect on the venules and small veins as well. Attenuation of this particular effect appears to be the main alteration occurring during long-term treatment since the peripheral vascular resistance tends to decrease further. This would explain both the considerable increase in stroke volume and cardiac output, again most pronounced during resting conditions, and the presence of postural hypotension during the acute experiment but not after long-term treatment. On the other hand, the additional decrease in resting (supine and upright) heart rates suggests a greater influence of the beta-receptor blocking action after long-term therapy.

As previously mentioned, adaptive structural changes appear early in the course of hypertension in the precapillary section of the vascular system and the left heart (Folkow, 1975). The precapillary structural adjustment taking the form of an increased wall lumen ratio implies a mutual reinforcement between functional and structural factors, resulting in exaggerated increases of resistance and arterial pressure, for given increases of vascular smooth muscle activity. Furthermore, evidence has recently been provided that both acute and prolonged adrenoceptor blockade results in increased blood levels of adrenaline and noradrenaline. This has been shown to apply not only to non-selective beta-receptor blockers such as propranolol (Trap-Jensen *et al.*, 1976b) and cardioselective agents such as metoprolol (Koch, unpublished data), respectively, but also to labetalol (Koch, 1978). Raised levels of circulating noradrenaline may be an important factor contributing to the increased vascular resistance regularly observed during acute and short-term beta-receptor blockade, particularly with non-selective antagonists, and to the failure of the vascular resistance to decrease significantly below pretreatment levels during long-term therapy. This implies that additional alpha-receptor blockade is a prerequisite for peripheral vascular resistance to be distinctly lowered and a definite advantage with respect to the interaction between structural changes and functional excitatory influences.

The comparison of intravenous and oral labetalol in this series shows that considerably higher oral doses are required to achieve a blood pressure reduction similar to that obtained with 50 mg intravenous labetalol. This is obviously mainly caused by a considerable first-pass metabolism that reduces bioavailability to about 40 per cent (Brogden *et al.*, 1978). This explains also the need for frequent dose readjustment in the initial stage of treatment if therapy is started with relatively low doses as was the case in this series (Koch, 1976c). However, the fairly high doses (2400 mg daily) that had to be used in some of these patients who had not satisfactorily responded to previous treatment with different antihypertensive regimens, were in all cases well tolerated. The complete lack of troublesome side-effects attributable to the drug after a 3-year continuous treatment in this series is noteworthy.

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Non-invasive assessment of left ventricular response to Valsalva manoeuvre in normal and diabetic subjects using praecordial accelerocardiography

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SUMMARY The left ventricular response to the Valsalva manoeuvre was studied in 5 normal subjects (group 1), 6 diabetics without autonomic neuropathy (group 2), and 5 diabetics with autonomic neuropathy (group 3), using the maximum amplitude of the praecordial accelerocardiogram (DE) as a non-invasive index of left ventricular performance.

During the Valsalva manoeuvre DE decreased in all 3 groups. In groups 1 and 2, DE increased significantly above the control value after release of the manoeuvre (DE overshoot) but this did not occur in group 3. It is suggested that the overshoot of DE in groups 1 and 2 reflects an increase in left ventricular contractility after release of the Valsalva manoeuvre and the absence of an overshoot in DE in the patients with autonomic neuropathy is the result of loss of cardiac adrenergic innervation.

The ability to detect an abnormal cardiovascular response to the Valsalva manoeuvre using the non-invasive technique of praecordial accelerocardiography may be of practical value in the assessment of left ventricular function.

Praecordial accelerocardiography is a useful non-invasive technique for detecting changes in peak acceleration of aortic blood flow, which itself is a sensitive measure of left ventricular performance (Reuben and Littler, 1973).

There is normally an increase in left ventricular contractility after release of the Valsalva manoeuvre (Mason *et al.*, 1970; Brooker *et al.*, 1974) but the haemodynamic response to the manoeuvre is often impaired in patients with heart disease (Elisberg, 1963). An abnormal cardiovascular response to the Valsalva manoeuvre also occurs commonly in patients with diabetic autonomic neuropathy (Sharpey-Schafer and Taylor, 1960; Lloyd-Mostyn and Watkins, 1975).

The present study was designed to see whether the changes in left ventricular contractility during and after the Valsalva manoeuvre could be detected non-invasively using praecordial accelerocardiography in normal subjects and to compare this with the left ventricular response in diabetic patients with known autonomic neuropathy.

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Subjects and methods

The patients studied were 5 normal male subjects (group 1), 6 male diabetics with no clinical features of autonomic neuropathy or other diabetic complications and with a normal Valsalva ratio (group 2), and 5 male diabetics with clinical features of autonomic neuropathy (postural hypotension in 4, abnormal sweating in 4, diarrhoea in 4, gastric fullness in 2, hypoglycaemic unawareness in 2) (group 3); all of the latter had an abnormal Valsalva ratio and sustained handgrip response (Ewing *et al.*, 1973). In group 1 the mean age was 47 (range 35 to 60) years, in group 2 it was 45 (range 21 to 54) years, and in group 3 it was 43 (range 28 to 65) years. The mean duration of diabetes in group 2 was 19 (range 7 to 36) years and in group 3 it was 20 (11 to 29) years. All but 2 of the diabetics were insulin-dependent. None of the normal or diabetic subjects had clinical, electrocardiographic, or radiological evidence of cardiovascular disease.

The praecordial accelerocardiogram transducer, which has been described in detail previously (Reuben and Littler, 1973; Hume *et al.*, 1975), was attached by an adhesive disc to the chest wall overlying the fifth rib at a point medial to the apex beat. A simultaneous electrocardiogram was recorded with the accelerocardiogram on the second channel of an ultraviolet recorder.

The subjects performed a standardised Valsalva manoeuvre while lying supine by blowing into a mouthpiece attached to a manometer and maintaining a pressure of 40 mmHg for 15 seconds (Ewing *et al.*, 1973). The electrocardiogram and accelerocardiogram were recorded continuously for 15 seconds before, during, and for 20 cardiac cycles after release of the manoeuvre.

In each subject the RR interval and maximum amplitude of the accelerocardiogram (DE deflection according to labelling of Luisada, 1962, which occurs at the onset of ejection) were averaged over 10 consecutive cardiac cycles immediately preceding the onset of the Valsalva manoeuvre in order to obtain control values. The RR interval and DE were also averaged over the last 5 beats before release of the Valsalva strain. After release the RR interval and DE were measured individually for the next 20 beats. The RR interval and DE during and after the Valsalva manoeuvre were expressed as a percentage of the control value. No attempt was made to calibrate the tracings in absolute units of acceleration because individual variations in chest wall thickness and transducer coupling mean that the absolute value of DE has no physiological significance.

The significance of the changes in DE during the Valsalva manoeuvre within each group was calculated by Student's paired t test, using the original measurements of DE. When comparing the percentage changes in DE during the Valsalva manoeuvre between the different groups, one-way analysis of variance was used.

Results

The Table shows the mean RR interval and DE in each group during the Valsalva manoeuvre and for 20 beats after release, expressed as a percentage of the control value. Fig. 1 is an example of a normal response and Fig. 2 shows the time relation of the changes in RR interval and DE in the different groups. As can be seen from Fig. 2, the pattern of response in terms of RR interval and DE was similar in groups 1 and 2.

RR INTERVAL (Table; Fig. 2)
In all 3 groups the mean RR interval decreased during the Valsalva manoeuvre. Immediately on release there was a further small decrease lasting 4 to 5 beats, after which the RR interval increased to reach the control value by beat 7 to 11 in groups 1 and 2. Whereas the RR interval increased above the control value in groups 1 and 2, reaching a maximum between beats 13 and 20, in group 3 no increase in RR interval above the control value was observed after release of the Valsalva manoeuvre.

Table *Group mean changes in RR interval and DE during Valsalva manoeuvre (expressed as percentage of control mean value)*

	Strain† period	*Post-strain period† Beat after release*																			
		1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*	*13*	*14*	*15*	*16*	*17*	*18*	*19*	*20*
RR interval		Group 1 (n = 5)																			
Mean	75	73	69	72	73	77	95	101	99	102	109	113	113	109	119	122	124	124	127	124	127
SD	11	10	13	17	7	10	28	30	26	27	31	27	24	27	23	24	25	22	23	22	23
		Group 2 (n = 6)																			
Mean	80	80	80	80	78	78	80	81	83	94	102	109	111	130	123	130	122	123	124	122	118
SD	6	7	7	7	6	6	7	5	4	11	16	23	19	33	19	17	11	16	15	14	10
		Group 3 (n = 5)																			
Mean	94	94	91	94	90	95	95	95	96	95	96	97	95	96	96	98	98	97	99	99	96
SD	6	5	7	5	10	3	5	5	5	3	3	5	8	3	3	7	6	5	5	5	5
DE deflection		Group 1																			
Mean	43‡	79	86	109	125*	162‡	154‡	139‡	139‡	128*	125	124	119	122	125	117	122	123	114	110	105
SD	21	28	32	60	31	34	17	7	15	25	31	27	27	26	41	31	33	34	36	34	31
		Group 2																			
Mean	74*	93	89	104	136*	140*	140*	150§	145§	137*	133	121	130	132	122	114	124	122	104	117	127
SD	39	17	28	29	33	46	46	44	37	34	47	27	33	32	36	26	30	28	15	19	33
		Group 3																			
Mean	67*	104	102	107	99	110	106	100	106	103	108	105	108	115	109	107	114	110	106	106	109
SD	18	29	31	29	13	22	8	16	14	18	32	13	14	14	15	11	12	21	12	12	11

†Values of RR and DE expressed as a percentage of the average value for 10 consecutive cardiac cycles immediately preceding the Valsalva strain.
During strain period RR and DE are expressed as average of values for 5 consecutive cardiac cycles immediately before release of Valsalva.
Significance of change from control value, * $P < 0{\cdot}05$; § $P < 0{\cdot}01$; ‡ $P < 0{\cdot}001$.

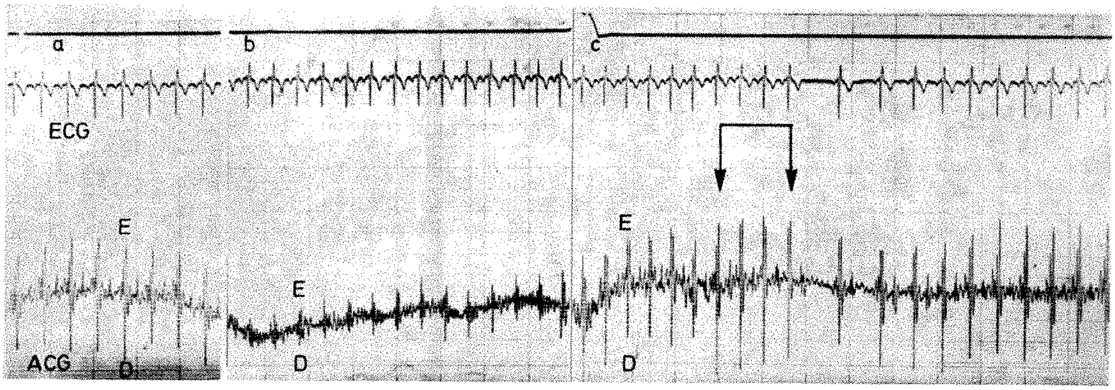

Fig. 1 *Example of a normal response to the Valsalva manoeuvre.* (a) *Before Valsalva strain.* (b) *During Valsalva strain.* (c) *After release of Valsalva strain. ECG, electrocardiogram; ACG, praecordial accelerocardiogram; DE, maximum systolic deflection of accelerocardiogram. Note decrease in DE during Valsalva manoeuvre* (b) *and overshoot after release* (c *between arrows*) *preceding bradycardia.*

MAXIMUM AMPLITUDE OF ACCELEROCARDIOGRAM (DE) (Table ; Fig. 2)

In all 3 groups the mean value of DE decreased significantly during the Valsalva manoeuvre (group 1 $P < 0{\cdot}001$; group 2 $P < 0{\cdot}05$; group 3 $P < 0{\cdot}05$). After release, DE increased to reach the control value within 3 beats in all 3 groups. Thereafter the mean value for DE increased significantly above the control value from beats 4 to 9 inclusive in groups 1 and 2, before decreasing again. All 11 subjects in groups 1 and 2 showed this characteristic 'overshoot' in DE. In group 3 no significant increase over the control value of DE occurred at any time after release of the Valsalva manoeuvre in the group as a whole, though 1 subject in this group did show an 'overshoot' in DE after release of the manoeuvre (that is a value greater than control mean + 2 standard deviations of the mean).

When the 3 groups were compared using analysis of variance no significant difference was found between them in the magnitude of the decrease in DE during the Valsalva manoeuvre ($P > 0{\cdot}05$). After release DE was significantly greater in groups 1 and 2 than in group 3 from beats 4 to 8 inclusive ($P < 0{\cdot}05$ in each case).

Discussion

The beat-to-beat changes in RR interval during and after the Valsalva manoeuvre in the normal subjects and the diabetics without autonomic neuropathy in this study are similar to those described previously in normal subjects (Flessas *et al.*, 1970). The response in the diabetics with autonomic neuropathy is also in agreement with previous observations in similar patients (Lloyd-Mostyn and Watkins, 1975).

In addition, the present study shows that the maximum amplitude of the praecordial accelerocardiogram (DE) consistently decreased during the Valsalva manoeuvre and increased significantly above the control value after release (that is 'overshoot') in the normal subjects and the diabetics without autonomic neuropathy. In the diabetics with autonomic neuropathy there was a similar decrease in DE during the Valsalva manoeuvre but no significant increase above the control value occurred after release.

Changes in DE have been shown to correlate closely with changes in the peak acceleration of blood flow in the ascending aorta in dogs during a wide range of manoeuvres (Reuben and Littler, 1973). Peak acceleration of aortic flow, in turn, is very sensitive to changes in left ventricular contractile state induced in dogs by coronary artery occlusion or the administration of various drugs (Noble *et al.*, 1966; Nutter *et al.*, 1971; Reuben and Littler, 1973). The praecordial accelerocardiogram therefore appears to be a useful non-invasive technique for detecting changes in left ventricular performance (Reuben and Littler, 1973).

The effects of the Valsalva manoeuvre on DE in the normal subjects and the diabetics without autonomic neuropathy in this study are in agreement with previous catheterisation studies in which peak aortic blood flow and peak velocity of aortic flow were measured. These indices of left ventricular pump performance were shown to decrease during the Valsalva manoeuvre and to increase above control values after release (Fox *et al.*, 1966;

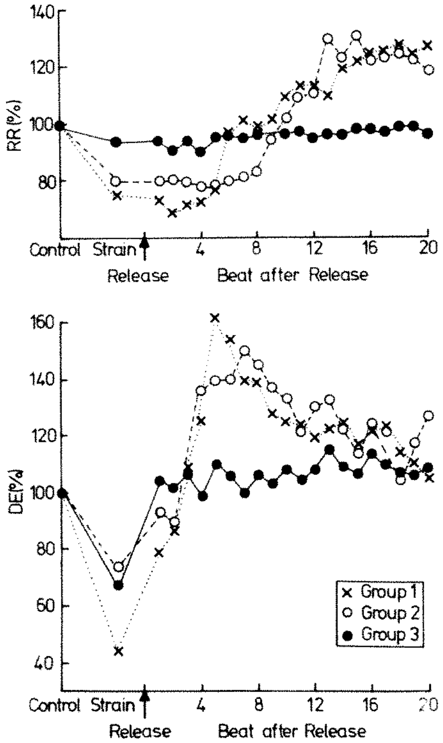

Fig. 2 *Group mean changes in RR interval and DE during and after Valsalva manoeuvre. Crosses (group 1), normal subjects; open circles (group 2), diabetics without autonomic neuropathy; closed circles (group 3), diabetics with autonomic neuropathy. Note DE overshoot in groups 1 and 2 precedes reflex bradycardia.*

Greenfield *et al.*, 1967; Mason *et al.*, 1970). Furthermore, the time course of the 'overshoot' in DE after release of the Valsalva manoeuvre in this study was similar to that observed in peak aortic flow velocity measured in normal subjects at cardiac catheterisation (Greenfield *et al.*, 1967).

Although the decrease in DE during the Valsalva manoeuvre in this study may have been partly the result of a change in the coupling between the heart and chest wall during the forced expiration, the magnitude of the decrease was strikingly similar to that which occurred in peak aortic flow velocity measured at cardiac catheterisation during the Valsalva manoeuvre (Greenfield *et al.*, 1967; Mason *et al.*, 1970). Some observers have attributed the decline in left ventricular pump function during the Valsalva manoeuvre observed in catheterisation studies to the combined effects of increased systemic vascular resistance and reduced left ventricular filling during the manoeuvre (Mason *et al.*, 1970). It seems unlikely, however, that the increase in systemic vascular resistance during the Valsalva manoeuvre could account for the decrease in DE observed in this study because peak aortic accleration and DE are not influenced by sustained increases in systemic vascular resistance induced by vasoconstrictor drugs (Nutter *et al.*, 1971; Reuben and Littler, 1973). Though it is possible that decreases in left ventricular filling and left ventricular end-diastolic volume during the Valsalva manoeuvre (Brooker *et al.*, 1974) may have contributed to the decrease observed in DE, the effect, if any, of changes in left ventricular filling on peak aortic acceleration is controversial (Noble *et al.*, 1966; Nutter *et al.*, 1971; Reuben and Littler, 1973).

After release of the Valsalva manoeuvre left ventricular end-diastolic volume does not increase above the control value (Brooker *et al.*, 1974) and systemic vascular resistance remains increased (Elisberg, 1963). Consequently the 'overshoots' in peak aortic blood flow and peak aortic flow velocity observed in normal subjects at cardiac catheterisation (Fox *et al.*, 1966; Greenfield *et al.*, 1967; Mason *et al.*, 1970) indicate an increase in left ventricular contractile state after release of the Valsalva manoeuvre which was shown in this study using the non-invasive technique of praecordial accelerocardiography.

The absence of an 'overshoot' in DE after release of the Valsalva manoeuvre in the diabetics with autonomic neuropathy suggests that such patients are unable to increase left ventricular contractile state at this time. This may contribute to the impairment or absence of the normal overshoot in blood pressure which is frequently observed in such patients (Sharpey-Schafer and Taylor, 1960) because the presence of a normal blood pressure overshoot depends upon the ability of the left ventricle to increase cardiac output as well as on the patient's ability to increase systemic vascular resistance during and after the Valsalva manoeuvre (Elisberg, 1963). The inability of the diabetic patients with autonomic neuropathy to increase left ventricular contractility after release of the Valsalva manoeuvre is probably caused by loss of cardiac adrenergic innervation. It has been shown that such patients often have a reduced catecholamine response to tilting associated with a subnormal increase in heart rate, suggesting that cardiac adrenergic nerve function is impaired (Christensen, 1972). The contribution which beta-adrenergic stimulation makes to the heart rate changes during the Valsalva manoeuvre in normal subjects is not clear (Elisberg, 1963; Leon *et al.*, 1970), but beta-adrenergic blockade has been shown to abolish the overshoot in blood pressure (Prichard and Gillam, 1966) and may even convert a normal response into the 'square wave' type of response which is characteristic of patients with impaired left ventricular function (Vogel and Blount, 1967). These observations suggest that the beta-adrenergic nervous system is involved in the normal inotropic response to the Valsalva manoeuvre.

This study shows that it is possible to detect changes in left ventricular performance during the Valsalva manoeuvre in normal subjects and also to detect an impaired haemodynamic response in diabetics with autonomic neuropathy using the non-invasive technique of praecordial accelerocardiography. Since impairment of the left ventricular response to the Valsalva manoeuvre is helpful in the assessment of cardiac function (Mason *et al.*, 1970; Brooker *et al.*, 1974) this technique may find a clinical application in the evaluation of cardiac patients.

We are grateful to Dr R. J. Prescott for statistical advice.

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Pre- and postoperative left ventricular contractile function in patients with aortic valve disease[1]

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SUMMARY In 43 patients left ventricular micromanometry and cineangiography were performed preoperatively and 20 months after aortic valve replacement. A score of left ventricular functional impairment, derived from 5 to 8 haemodynamic variables, was calculated as: number of pathological indices × 100/total number of determined indices. Preoperatively the score of left ventricular functional impairment amounted to 35 per cent in group 1 (aortic stenosis: $n = 19$), to 61 per cent in group 2 (combined lesion: $n = 15$) ($P < 0{\cdot}05$), and to 87 per cent in group 3 (aortic regurgitation: $n = 9$) ($P < 0{\cdot}001$). In contrast, the functional classification according to the NYHA showed similar impairment in the 3 groups. Postoperatively the score of left ventricular functional impairment decreased significantly in all 3 groups to 10, 16, and 27 per cent, respectively, but the score of group 3 remained raised ($P < 0{\cdot}05$) as compared with that of group 1. The patients with residual left ventricular dysfunction had a higher preoperative left ventricular muscle mass than the patients with normal or near normal postoperative left ventricular function.

It is concluded that (1) at similar functional impairment according to the NYHA classification left ventricular contractile function is more severely impaired in aortic regurgitation and in aortic regurgitation + aortic stenosis than in aortic stenosis alone, (2) left ventricular function improves significantly after valve replacement in all three forms of aortic valve disease, (3) residual functional impairment is greater in aortic regurgitation than in aortic stenosis or aortic stenosis + aortic regurgitation, and (4) persistent postoperative left ventricular functional impairment is found in the patients with severe preoperative hypertrophy.

The outcome of aortic valve replacement with respect to mortality and long-term postoperative thromboembolic complications has been the subject of numerous reports (Björk *et al.*, 1974; Hirshfeld *et al.*, 1974; Isom *et al.*, 1974; Earnhorst *et al.*, 1975; Rothlin *et al.*, 1977) but there is only limited information regarding myocardial function after successful surgery (Gault *et al.*, 1970; Doces *et al.*, 1974; Schmutzler *et al.*, 1976). However, the postoperative quality of life and ultimately the fate of the patient with aortic valve disease is determined by the functional state of the left ventricular myocardium. Thus it is important to know to what extent preoperatively compromised left ventricular function is reversible after surgery. Obviously this would influence our indications for valve replacement, which, in most centres at present, are based essentially on the patient's complaints. The relation of overall functional limitation (NYHA classification) to the actual myocardial function may vary in different forms of aortic valve disease. It was the purpose of the present study to compare preoperative left ventricular function with that after surgery in patients with aortic stenosis, aortic regurgitation, and combined aortic valve disease. We assessed in the same groups the relation of preoperative invasive left ventricular function to the overall functional impairment according to the NYHA classification. We also studied procedures thought to be useful for myocardial protection during surgery to see whether they had any impact on the long-term contractile state of the left ventricular myocardium.

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e 1 *Clinical data*

	Age (y) *Preop*	*Postop*	*NYHA class* *Preop*	*Postop*	*PWC (% of normal)* *Preop*	*Postop*	*SOKI (mV)* *Preop*	*Postop*	*Restudy (mth) postop*	*Comments*
p 1 (aortic stenosis)	52 ± 8	54 ± 8	2·8 ± 0·6	1·4 ± 0·6	70 ± 26	87 ± 14	4·8 ± 1·2	3·5 ± 1·2	16·6 ± 5·9	1 PDA; 2 LBBB, 1 RBBB
ɔer	19	19	19	19	18	19	16	16	19	Cor. arteriography in 16/19 patients
			< 0·001		< 0·02		< 0·001			
p 2 (aortic stenosis regurgitation)	44 ± 9	46 ± 9	2·7 ± 0·6	1·4 ± 0·5	70 ± 18	88 ± 16	6·2 ± 2·1	3·8 ± 1·2	20·7 ± 8·8	1 LAD stenosis 75%, 1 VSD, 1 LBBB
ber	15	15	15	15	15	15	14	14	15	Cor. arteriography in 11/15 patients
			< 0·001		< 0·01		< 0·001			
p 3 (aortic gurgitation)	41 ± 9	43 ± 10	2·4 ± 0·5	1·3 ± 0·5	67 ± 22	86 ± 18	5·8 ± 1·6	3·6 ± 0·8	26·0 ± 14·2	1 LBBB
ber	9	9	9	9	8	9	8	8	9	Cor. arteriography in 2/9 patients
			< 0·01		< 0·025		< 0·005			
s 2	< 0·01		NS	NS	NS	NS	< 0·05	NS	NS	
s 3	< 0·005		NS	NS	NS	NS	NS	NS	< 0·02	
s 3	NS	NS	NS	NS	NS	NS	NS	NS	NS	

, physical working capacity; SOKI, Sokolow index for left ventricular hypertrophy ($SV_1 + RV_{5 \text{ or } 6}$); PDA, persistent ductus arteriosus; LBBB and B, left and right bundle-branch block; LAD, left anterior descending coronary artery; VSD, ventricular septal defect; P, probability (paired t test); robability (unpaired t test); NS, not significant.

Subjects and methods

PATIENTS

Forty-three patients (39 men; 4 women) with aortic valve disease were evaluated by right and left heart catheterisation and cineangiography before operation and 20 (range 11 to 55) months after aortic valve replacement (Table 1). Group 1 consisted of 19 patients with aortic stenosis. These patients had a mean systolic pressure gradient across the aortic valve between 51 and 131 mmHg and none or only slight aortic regurgitation (regurgitation fraction as determined by thermodilution < 0·18). Group 2 consisted of 15 patients with a combined aortic valve lesion (mean systolic pressure gradient 28 to 87 mmHg, aortic regurgitation fraction 0·22 to 0·70). In group 3 there were 9 patients with aortic regurgitation (regurgitation fraction 0·58 to 0·84). Coronary arteriography was carried out in 29 patients. In only one patient in group 2 was there a significant (>50%) coronary arterial stenosis. Of the 14 patients in whom the coronary arteries were not visualised selectively, 10 were below the age of 43 years. Associated minor valvular or congenital lesions included minimal to slight mitral regurgitation in 17 patients, persistent ductus arteriosus in 1, and ventricular septal defect in 1.

All patients were in sinus rhythm before and after operation. Apart from 5 patients who showed a stable left or right bundle-branch block, the duration of the QRS complex was within normal limits. Patients in whom a bundle-branch block appeared after surgery were excluded from the study. Most patients were on maintenance digitalis before and/or after valve replacement. Overall physical working capacity was evaluated by bicycle ergometry in the sitting position. The achieved number of watts at the submaximal heart rate was expressed as a percentage of the normal value for a given height, age, and sex.

CATHETERISATION AND CINEANGIOGRAPHY

Informed consent was obtained from all patients. Premedication consisted of 10 mg chlordiazepoxide or 5 mg diazepam given orally 1 hour before the procedure. Left ventricular pressure was measured in 32 patients by a transseptally introduced micromanometer (Statham SF-1 or Millar) at both pre- and postoperative catheterisation. In 5 patients micromanometer measurements were obtained solely at the postoperative study. In six patients only conventional left ventricular pressure measurements were obtained. From the high fidelity left ventricular curves that were recorded at a paper speed of 200 mm/s (oscillograph Electronics for Medicine DR/16) the first derivative (dP/dt) and the instantaneous quotient (dP/dt)/P were obtained by an analogue computer (Krayenbuehl *et al.*, 1973). The peak value of (dP/dt)/P was labelled Vpm (peak measured velocity of shortening) and expressed in muscle lengths (ML)/s, a constant of series elasticity of 28 being used (Mirsky *et al.*, 1971). Total pressure Vmax was determined by linear extrapolation of the descending limb of the pressure-velocity curves (Krayenbuehl *et al.*, 1973). This was done only when at least 3 data points on the descending limb before aortic valve opening were available.

Monoplane left ventricular cineangiography in the right anterior oblique position was performed at midinspiration at a fiming rate of 50 or 75 frames per second. Quantitative evaluation of end-diastolic and end-systolic frames for the calculation of end-diastolic volume, ejection fraction, mean normalised systolic ejection rate, and mean velocity of endocardial circumferential shortening was carried out as reported previously (Brunner *et al.*, 1977). End-diastolic wall thickness was determined in most instances from a second left ventricular cineangiogram obtained in the anteroposterior position or occasionally from the first angiogram in the right anterior oblique position. Left ventricular muscle mass was calculated according to the technique of Rackley *et al.* (1964).

ASSESSMENT OF LEFT VENTRICULAR CONTRACTILE FUNCTION

Isovolumic as well as ejection phase indices have been used for quantifying the functional state of the left ventricular myocardium. However, no single index is valid under all haemodynamic conditions (Peterson *et al.*, 1974; Kreulen *et al.*, 1975; Brunner *et al.*, 1977). Therefore, a score derived from 5 to 8 variables including left ventricular end-diastolic pressure, cardiac index, end-diastolic volume index, ejection fraction, mean velocity of endocardial circumferential shortening, mean normalised systolic ejection rate, peak measured velocity of shortening, and total pressure Vmax was established for describing left ventricular contractile function. The score of left ventricular functional impairment was calculated as: number of pathological indices × 100/total number of determined indices. Table 2 indicates the criteria when a given index of left ventricular function was considered to be pathological (Brunner *et al.*, 1977). The total number of determined indices included all 8 variables in 60 instances, 7 variables in 8 instances, 6 in 17 instances, and 5 in 1 instance.

Table 2 *Indices used for establishing score of left ventricular functional impairment*

	Pathological when:
Left ventricular end-diastolic pressure (mmHg)	> 12
Cardiac index (l/min per m²)	< 2·5
End-diastolic volume index (ml/m²)	> 121
Ejection fraction	< 0·62
Mean velocity of circumferential fibre shortening (circ/s)	< 1·00
Mean normalised systolic ejection rate (EDVs/s)	< 2·00
Vpm (ML/s)	< 1·14
Vmax (ML/s)	< 1·47

Vpm, peak measured velocity of contractile element shortening; Vmax, extrapolated maximal velocity of contractile element shortening; EDV, end-diastolic volume; circ, circumferences.

SURGICAL PROCEDURE (Table 3)

A Björk-Shiley prosthesis (no. 19 to 31, average tissue annulus diameter 25·2 ± 2·1 mm) was inserted in 32 patients, and a Lillehei-Kaster (no. 16 to 20, average tissue annulus diameter 25·0 ± 1·8 mm) prosthesis was inserted in 11 patients. Postoperative paravalvular leakage occurred in only 1 patient of group 2 who had a postoperative aortic regurgitation fraction of 0·30. In 1 patient an aortocoronary bypass to the left anterior descending coronary artery was carried out but was found to be occluded at the postoperative evaluation. A persistent ductus arteriosus and a small ventricular septal defect were closed. Myocardial protection during cardiopulmonary bypass consisted of (1) 30° anoxic arrest (n = 13), (2) coronary flush with 1000 ml 4° Ringers solution (n = 24), and (3) biochemical cardioplegia* (n = 6). In order to evaluate possible intraoperative damage, a score including intraoperative events and early postoperative complications was established (Table 4). The scoring technique was such that at a high score there was an increased probability of intraoperative myocardial damage.

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* 200 ml Cardioplegin (Dr Frank Köhler Chemie, Alsbach, West Germany) injected directed into the coronary arteries.

Table 3 *Surgical data*

	Björk-Shiley	*Lillehei-Kaster*	*30° anoxic arrest*	*Cold coronary flush*	*Biochemical cardioplegia*	*Comments*
Group 1 (aortic stenosis) (n = 19)	13	6	7	10	2	Closure of PDA in 1 patient
Group 2 (aortic stenosis + regurgitation) (n = 15)	13	2	4	10	1	Closure of VSD in 1 patient; ACBP in 1 patient occluded at postop study
Group 3 (aortic regurgitation) (n = 9)	6	3	2	4	3	

PDA, persistent ductus arteriosus; VSD, ventricular septal defect; ACBP, aortocoronary bypass.

Table 4 *Score for the evaluation of intraoperative myocardial damage*

	Score points		
	1	*2*	*3*
Crossclamping of aorta			
In anoxic arrest and cold coronary flush	< 40 min	40 to 60 min	> 60 min
In biochemical cardioplegia	< 50 min	50 to 70 min	> 70 min
Duration of cardiopulmonary bypass	< 70 min	70 to 90 min	> 90 min
Emergency operation	No	Yes	
Hypotension before cardiopulmonary bypass	No	Yes	
Number of defibrillations	1 to 2	3 to 5	> 5
Duration of bypass support after beginning of coronary reperfusion	< 20 min	20 to 30 min	> 30 min
Duration of intubation	< 2 d	2 to 4 d	> 4 d
Postoperative catecholamines	< 12 h	12 to 48 h	> 48 h

Results

CLINICAL DATA

Overall functional limitation, according to the classification of the NYHA, and the reduction of ergometric physical working capacity were similar in the 3 groups of patients before operation. After aortic valve replacement there was a significant improvement in both the NYHA score and the physical working capacity in all groups (Table 1). Left ventricular hypertrophy as assessed by the Sokolow index was highest before operation in group 2. After operation this index decreased significantly in all 3 groups, and the postoperative mean values were at or slightly above the upper limit of normal (3·5 mV).

LEFT VENTRICULAR FUNCTION

(Tables 5 and 6)

Before operation the left ventricular end-diastolic pressure was raised in all 3 groups but the increase was significantly larger in groups 2 and 3 than in group 1. After operation the end-diastolic pressure decreased significantly to values in the upper range of normal. The end-diastolic volume index before operation was increased in groups 2 and 3 and was in the upper range of normal in group 1. After operation there was a significant decrease in end-diastolic volume index in all 3 groups, the extent of reduction being largest in the patients with aortic regurgitation who had the largest preoperative ventricular volume. Cardiac index did not differ significantly between the 3 groups before operation and remained unchanged after surgery. Preoperatively the isovolumic (peak measured velocity of shortening, Vmax) as well as the ejection phase (ejection fraction, mean normalised systolic ejection rate, and mean velocity of endocardial circumferential shortening) indices were normal or only slightly depressed in group 1 (aortic stenosis) but were clearly pathological in group 3 (aortic regurgitation). In group 2 (aortic stenosis and regurgitation) the indices of left ventricular contractile function were intermediate. After operation there was a significant increase in practically all contractile indices. However, normalisation was generally less complete in aortic regurgitation than in aortic stenosis; again the patients with the combined lesion showed intermediate values.

Before operation the score of left ventricular functional impairment was highest in aortic regurgitation, lowest in aortic stenosis, and intermediate in aortic stenosis plus regurgitation (Fig. 1). After aortic valve replacement there was a significant reduction of the score of left ventricular functional impairment in all 3 groups. Though the extent of decrease was largest in aortic regurgitation the score remained significantly raised in aortic regurgitation as compared with aortic stenosis (Fig. 1). Thus, there was a residual postoperative impairment of left ventricular contractile function in the patients with aortic regurgitation.

PREOPERATIVE LEFT VENTRICULAR FUNCTION AND FUNCTIONAL CLASSES ACCORDING TO NYHA

There was no close correlation between the overall functional limitation (NYHA class) and the impairment of left ventricular contractile function. At a given NYHA class the score of left ventricular functional impairment was significantly greater in aortic regurgitation than in aortic stenosis whereas the values for the patients with combined aortic valve lesion were intermediate (Fig. 2).

SCORE OF POTENTIAL INTRAOPERATIVE DAMAGE, MEASURES OF INTRAOPERATIVE MYOCARDIAL PROTECTION, AND POSTOPERATIVE LEFT VENTRICULAR FUNCTION

The score of potential intraoperative damage amounted to 11·2 points in group 1, to 13·3 points in group 2 ($P < 0{\cdot}01$ vs. group 1), and to 12·6 points in group 3 (not significantly different as com-

Table 5 *Haemodynamic data*

	Left ventricular peak systolic pressure (mmHg)		*Left ventricular end-diastolic pressure (mmHg)*		*Heart rate (bpm)*		*Cardiac index (l/min per m²)*	
	Preop	*Postop*	*Preop*	*Postop*	*Preop*	*Postop*	*Preop*	*Postop*
Group 1 (aortic stenosis)	220 ± 33	161 ± 31	21 ± 7	13 ± 3	76 ± 19	79 ± 16	3·1 ± 0·7	3·1 ± 0·
Number	19	19	19	19	19	19	19	19
P	< 0·001		< 0·001		NS		NS	
Group 2 (aortic stenosis + regurgitation)	185 ± 30	135 ± 18	29 ± 10	11 ± 3	73 ± 10	71 ± 10	2·9 ± 0·7	3·1 ± 0·
Number	15	15	15	15	15	15	15	15
P	< 0·001		< 0·001		NS		NS	
Group 3 (aortic regurgitation)	136 ± 10	136 ± 13	37 ± 16	10 ± 2	78 ± 15	72 ± 12	2·6 ± 1·1	3·0 ± 0·
Number	9	9	9	9	9	9	9	9
P	NS		< 0·001		NS		NS	
$P^{*}_{1\ vs\ 2}$	< 0·005	< 0·01	< 0·02	NS	NS	NS	NS	NS
$P^{*}_{1\ vs\ 3}$	< 0·001	< 0·05	< 0·001	< 0·025	NS	NS	NS	NS
$P^{*}_{2\ vs\ 3}$	< 0·001	NS	NS	NS	NS	NS	NS	NS

Vpm, peak measured velocity of contractile element shortening; Vmax, extrapolated maximal velocity of contractile element shortening; P, probability (paired t test); P*, probability (unpaired t test).

pared with groups 1 and 2). When the patients were grouped according to the measure of intraoperative myocardial protection (30° anoxic arrest, cold coronary flush, biochemical cardioplegia), there was no significant difference among these groups either with respect to the score of potential intraoperative damage or with respect to the postoperative score of left ventricular functional impairment. Comparison between the score of potentional intraoperative damage and the score of postoperative left ventricular functional impairment showed no significant correlation (correlation coefficient 0·10).

LEFT VENTRICULAR WALL THICKNESS AND MUSCLE MASS (Table 6)

In groups 1 and 2 the preoperatively increased left ventricular end-diastolic wall thickness decreased significantly after operation to values at or slightly larger than the upper limit of normal in our laboratory (1·04 cm (Brunner *et al.*, 1977)). In group 3 wall thickness remained unchanged after operation. Left ventricular muscle mass index decreased significantly in all 3 groups, the postoperative mean values reaching the upper limit of our normal range (50 to 129 g/m² (Brunner *et al.*, 1977)).

Discussion

PREOPERATIVE FINDINGS

With respect to the preoperative overall functional limitation the 3 subgroups of aortic valve disease appeared to be comparable because the average NYHA class and the ergometrically determined physical working capacity were of similar magnitude.

Table 6 *Angiographic data*

	Body surface area (m²)		*Left ventricular end-diastolic volume index (ml/m²)*		*Heart rate (bpm)*		*Ejection fraction*	
	Preop	*Postop*	*Preop*	*Postop*	*Preop*	*Postop*	*Preop*	*Postop*
Group 1 (aortic stenosis)	1·73 ± 0·13	1·76 ± 0·16	100 ± 35	82 ± 14	76 ± 16	80 ± 14	0·62 ± 0·19	0·72 ± 0
Number	19	19	19	19	19	19	19	19
P	NS		< 0·05		NS		< 0·02	
Group 2 (aortic stenosis + regurgitation)	1·77 ± 0·20	1·81 ± 0·20	158 ± 63	101 ± 44	78 ± 13	70 ± 12	0·57 ± 0·20	0·68 ±
Number	15	15	15	15	15	15	14	15
P	< 0·005		< 0·005		NS		< 0·025	
Group 3 (aortic regurgitation)	1·85 ± 0·18	1·89 ± 0·16	202 ± 49	105 ± 27	81 ± 13	77 ± 12	0·49 ± 0·09	0·64 ± 0
Number	9	9	9	9	9	9	9	9
P	< 0·05		< 0·001		NS		< 0·01	
$P^{*}_{1\ vs\ 2}$	NS	NS	< 0·005	NS	NS	NS	NS	NS
$P^{*}_{1\ vs\ 3}$	< 0·05	< 0·05	< 0·001	< 0·01	NS	NS	NS	< 0·02
$P^{*}_{2\ vs\ 3}$	NS	NS	NS	NS	NS	NS	NS	NS

P, probability (paired t test); P*, probability (unpaired t test); EDV, end-diastolic volume.

systolic pressure nt across aortic (mmHg)		*Aortic valve area (cm²)*		*max dP/dt (mmHg/s)*		*Vpm (ML/s)*		*Vmax (ML/s)*	
	Postop	*Preop*	*Postop*	*Preop*	*Postop*	*Preop*	*Postop*	*Preop*	*Postop*
19	19 ± 16	0·56 ± 0·15	1·05 ± 0·38	2230 ± 450	2120 ± 590	1·33 ± 0·23	1·70 ± 0·38	1·74 ± 0·32	2·13 ± 0·46
	19	19	13	16	18	16	18	16	18
·001				NS		< 0·001		< 0·005	
19	13 ± 9	1·14 ± 0·77	1·49 ± 0·39	1420 ± 350	1600 ± 310	0·87 ± 0·27	1·37 ± 0·30	1·34 ± 0·30	1·72 ± 0·37
	15	15	11	11	13	11	13	8	13
·001				< 0·02		< 0·001		< 0·02	
	11 ± 9		1·51 ± 0·43	1050 ± 200	1320 ± 160	0·77 ± 0·20	1·38 ± 0·21		1·67 ± 0·25
	9		6	6	5	6	5		5
				< 0·05		< 0·005			
1	NS	< 0·005	< 0·01	< 0·001	< 0·01	< 0·001	< 0·02	< 0·01	< 0·02
	NS		< 0·05	< 0·001	< 0·01	< 0·001	NS		< 0·05
	NS		NS	< 0·05	NS	NS	NS		NS

However, left ventricular contractile function was dissimilar in the three forms of aortic valve disease, the score of left ventricular functional impairment being significantly higher in aortic regurgitation and in combined valve lesion than in aortic stenosis (Fig. 1). This finding is important with respect to the indication of aortic valve surgery based on the patient's symptoms. It means that in aortic regurgitation and in combined aortic valve lesions deterioration of myocardial function is more advanced than in aortic stenosis when the patient becomes symptomatic and hence is selected for valve replacement. Thus, it is not surprising that long-term postoperative survival has been reported by several authors (Hirshfeld *et al.*, 1974; Isom *et al.*, 1974; Barnhorst *et al.*, 1975; Rothlin *et al.*, 1977) to be less favourable in aortic regurgitation and combined valve lesions than in aortic stenosis alone.

POSTOPERATIVE LEFT VENTRICULAR CONTRACTILE FUNCTION

In keeping with other postoperative haemodynamic studies in isolated aortic valve disease (Hultgren *et al.*, 1969; Kloster *et al.*, 1970; Lee *et al.*, 1970; Björk *et al.*, 1973a, b; Lurie *et al.*, 1977) left ventricular end-diastolic pressure returned to normal on average. Left ventricular ejection performance as assessed by the ejection fraction increased postoperatively to normal values in all 3 forms of aortic valve disease (Table 6). This observation is in agreement with other investigations (Doces *et al.*, 1974; Schmutzler *et al.*, 1976) dealing with angiographic assessment of left ventricular function after successful aortic valve replacement. In contrast, no significant postoperative change of left ventricular ejection fraction was reported in patients with aortic homografts (Kennedy *et al.*, 1968) or porcine

tion time (ms)		*Mean normalised systolic ejection rate (EDV/s)*		*Mean velocity of circumferential fibre shortening (circ/s)*		*Left ventricular end-diastolic wall thickness (cm)*		*Left ventricular muscle mass index (g/m²)*	
p	*Postop*	*Preop*	*Postop*	*Preop*	*Postop*	*Preop*	*Postop*	*Preop*	*Postop*
± 28	288 ± 28	1·96 ± 0·57	2·51 ± 0·29	1·05 ± 0·44	1·53 ± 0·28	1·18 ± 0·17	1·03 ± 0·14	154 ± 48	116 ± 28
	19	19	19	19	19	19	19	19	19
0·005		< 0·001		< 0·001		< 0·001		< 0·001	
± 35	293 ± 26	1·80 ± 0·67	2·36 ± 0·59	0·97 ± 0·51	1·38 ± 0·34	1·21 ± 0·17	1·07 ± 0·20	201 ± 48	132 ± 38
	15	14	14	15	15	15	15	15	15
:0·05		< 0·02		< 0·02		< 0·02		< 0·001	
± 18	291 ± 32	1·54 ± 0·28	2·23 ± 0·49	0·69 ± 0·28	1·25 ± 0·51	1·03 ± 0·26	1·04 ± 0·10	190 ± 76	130 ± 30
	9	9	9	9	9	9	9	9	9
:0·05		< 0·01		< 0·02		NS		< 0·02	
	NS	NS	NS	NS	NS	NS	NS	< 0·01	NS
	NS	< 0·05	NS	< 0·05	NS	NS	NS	NS	NS
	NS	NS	NS	NS	NS	< 0·05	NS	NS	NS

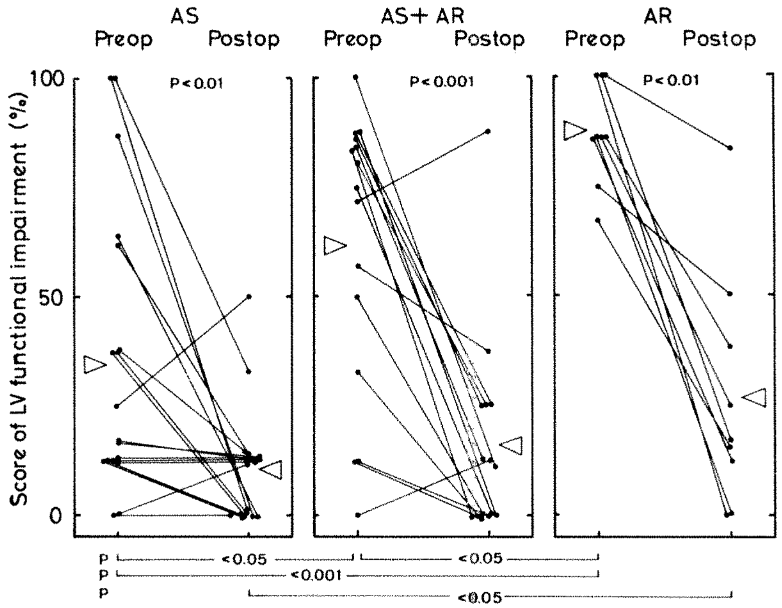

Fig. 1 *Score of left ventricular (LV) functional impairment in aortic stenosis (AS: group 1), in combined aortic stenosis and regurgitation (AS + AR: group 2), and in aortic regurgitation (AR: group 3). There is a significant decrease of LV functional impairment after aortic valve replacement (P values inside the 3 panels; paired t test). In AR the LV functional impairment is significantly greater than in AS before as well as after operation (P values below the 3 panels; unpaired t test). The triangles indicate the mean values.*

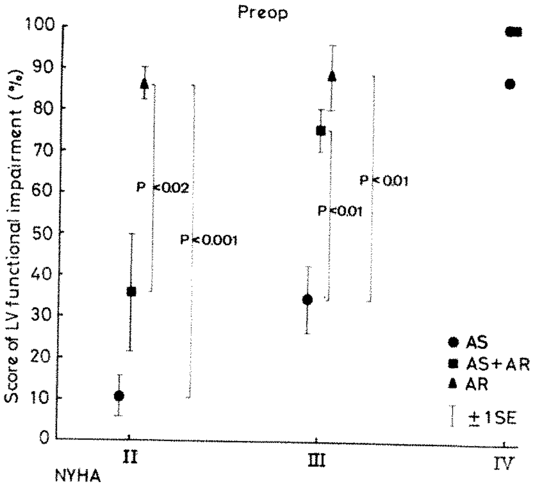

Fig. 2 *Score of left ventricular (LV) functional impairment at preoperative evaluation in the NYHA classes II, III, and IV. In the NYHA classes II and III the score of left ventricular functional impairment was significantly greater in aortic regurgitation (AR) than in aortic stenosis (AS). The score of the patients with combined aortic valve lesion (AS + AR) was intermediate. P = probability (unpaired t test). In the NYHA classes II and III the solid symbols represent mean values ± 1 standard error. In the NYHA class IV the symbols represent 3 single values (2 AS, 1 AS + AR).*

Table 7 *Score of potential intraoperative myocardial damage and preoperative muscle mass for three groups of patients*

	Score of left ventricular functional impairment (%)		*Score of potential intraop damage of myocardium (points)*	*Left ventricular muscle mass index Preop* (g/m^2)
	Preop	*Postop*		
Group A (n = 13)* (maximally 1 LV index pathological preop and postop)	10	8	11·6	163
Group B (n = 19)† (2 or more LV indices pathological preop, maximally 1 index pathological postop)	72	5	12·4	168
Group C (n = 11)‡ (2 or more LV indices pathological preop and postop)	78	44	12·6	213
$P_{A\ vs\ B}$			NS	NS
$P_{A\ vs\ C}$			NS	<0.05
$P_{B\ vs\ C}$			NS	<0.1

* Group A with minimal pre- and postoperative left ventricular (LV) functional impairment.
† Group B with depressed preoperative LV function and minimal postoperative impairment.
‡ Group C with depressed preoperative LV function and postoperative residual dysfunction.

heterografts (Lurie *et al.*, 1977) in whom there was at least some postoperative aortic regurgitation.

Although the ejection fraction is a popular and useful index for the assessment of left ventricular function and has been shown to be of predictive value in valvular heart disease (Cohn *et al.*, 1974) it only incompletely reflects left ventricular contractile state when the loading conditions change (Sonnenblick and Strobeck, 1977). After operation afterload decreased because left ventricular peak systolic pressure and/or left ventricular dimensions were reduced. Therefore, an appraisal of left ventricular function should include not only ejection indices but also standard haemodynamics and isovolumic velocity indices to give the best picture of the actual state of the myocardium. Thus, using for this purpose the score of left ventricular functional impairment, we found a remarkable improvement in left ventricular contractile function in all 3 groups after valve replacement (Fig. 1). Nevertheless there remained some residual functional impairment which was significantly greater in patients with aortic regurgitation than in those with aortic stenosis. The postoperative score of the patients with combined lesions was intermediate. These postoperative observations are at variance with those of Gault *et al.* (1970) who reported no improvement in contractile function in patients with free aortic regurgitation after operation.

Table 8 *Score of potential intraoperative damage (PID) and postoperative score of left ventricular functional impairment (LVFI) in relation to method of myocardial protection*

Myocardial protection	*Score of PID (points)*	*Score of LVFI* (%)	
		Preop	*Postop*
I. 30° anoxic arrest (n = 13)	13·0	47	11
II. Cold coronary flush (n = 24)	15·7	57	17
III. Biochemical cardioplegia (n = 6)	12·8	53	22

For all three scores statistical comparisons (unpaired t test) between groups I, II, and III yielded P values > 0·05.

POSSIBLE CAUSES FOR RESIDUAL LEFT VENTRICULAR DYSFUNCTION

Surgery itself may represent serious trauma to the myocardium and thus may in part account for the residual left ventricular dysfunction. In order to test this hypothesis we have regrouped the 43 patients in 3 subsets according to the level of pre- and postoperative left ventricular contractile function (Table 7). In group A pre- and postoperative left ventricular contractile function was normal or near normal; in group B preoperative function was depressed but there was complete or nearly complete postoperative normalisation; in group C preoperative function was equally compromised as in B, but postoperatively there was a residual left ventricular functional impairment. If surgery *per se* had been a significant factor in determining residual impairment of left ventricular function, the score of potential intraoperative damage should have been raised in group C. However there was no significant difference among the three subsets A, B, and C.

Moreover the type of myocardial protection used during operation appeared to have had no impact on the postoperative contractile function (Table 8).

In another attempt to identify a common preoperative factor in those patients who did not normalise left ventricular function postoperatively the extent of hypertrophy estimated from the magnitude of the left ventricular muscle mass index was determined in the subsets A, B, and C (Table

7). It was observed that the patients with normal or near normal postoperative left ventricular function (groups A and B) had a smaller preoperative muscle mass index than the patients with two or more pathological postoperative indices of left ventricular function (group C) regardless of whether or not the preoperative function was impaired (group B) or normal or near normal (group A). This finding supports the contention that in aortic valve disease massive preoperative hypertrophy, probably associated with fibrosis (Maron *et al.*, 1975), is an adverse factor for the normalisation of postoperative left ventricular contractile function.

CONCLUSIONS ON INDICATION FOR AORTIC VALVE REPLACEMENT

In the last few years the operative mortality of aortic valve replacement has decreased to 2 to 4 per cent and has even been abolished as reported recently (Karp and Lell, 1976). Therefore survival alone cannot any longer be considered to be the criterion for success (Galyean *et al.*, 1974). In our opinion a legitimate requirement in 1978 has to be a complete or nearly complete normalisation of left ventricular contractile function after surgery. However, this goal can only be achieved if preoperative impairment of left ventricular contractile function is not too far advanced. With this objective in mind it appears to be safe in aortic stenosis to wait until symptoms of class II to III (NYHA) occur. On the other hand, in aortic regurgitation a similar overall functional limitation is associated with significantly greater impairment of left ventricular function which is only partially reversible after operation. Thus, we recommend that aortic valve replacement should be carried out in patients with haemodynamically important aortic regurgitation as soon as mild symptoms occur.

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Electrocardiographic changes resembling myocardial ischaemia in asymptomatic men with normal coronary arteriograms

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SUMMARY T wave and ST segment abnormalities in 20 asymptomatic men aged 18 to 55 were investigated because they were identical with myocardial ischaemic changes, and the professional livelihood of the subjects was jeopardised.

Coronary arteriograms showed unobstructed arteries in all except one in whom a 50 per cent lesion of the left anterior descending artery was present. Left ventricular angiograms showed a normal contraction pattern. Ejection fractions were normal in 12 and increased in 8.

Three characteristic electrocardiographic patterns were observed: flat or inverted T waves in leads II, III, aVF, and V4 to 6 designated type 1; deep T inversion particularly evident in leads V2 to 5 designated type 2, and minor ST segment depression in the inferior and lateral leads without T changes designated type 3.

Characteristically, type 1 changes were temporarily suppressed by either beta-blockade or an overnight rest and were more abnormal in the standing position. Type 2 and 3 changes were relatively uninfluenced by these manoeuvres.

Maximal treadmill exercise tests were positive in 6 and borderline or negative in 14. When repeated after oxprenolol all tests were negative.

Echocardiograms showed asymmetric septal hypertrophy in 3 subjects (ratio of greater than 1·5 between ventricular septum and posterior left ventricular wall).

After normalisation by an overnight rest, type 1 T wave abnormalities were reproduced by intravenous adrenaline infusion (0·024 to 0·18 μg/kg/min) but not by noradrenaline or by adrenaline after prior administration of oxprenolol. When the T waves had remained deeply inverted before infusion despite rest (type 2) adrenaline infusion normalised them and again noradrenaline was without effect. This effect was also prevented by oxprenolol. Type 3 changes were uninfluenced by catecholamine infusion.

Plasma catecholamine estimations suggest that catecholamine hypersecretion and hypersensitivity may both be relevant, particularly the latter.

The apparent bimodal response of the ventricular myocardium to adrenaline infusion is not surprising since *in vitro* experiments suggest that reversal of T wave polarity in either direction may result from summation of changes in action potential duration in different parts of the heart. Such changes may be unimodal, that is both areas involved show lengthening or shortening of action potential duration, but by occurring at different rates may lead to a bimodal change in the differences in duration which generate the T wave.

The finding of T wave and ST segment abnormalities identical with myocardial ischaemic changes in routine electrocardiograms of asymptomatic and apparently healthy people presents a difficult medical and socioeconomic problem. For example, periodic electrocardiograms are a man-

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Table 1 *Routine electrocardiographic findings in RAF aircrew 1972-1975*

Findings	*No. of ECGs*	*% Total*	*No. of men*	*% Total*
ST and T changes	416	3·1	338	3·9
Incomplete RBBB	241	1·8	226	2·6
Arrhythmias	98	0·7	89	1·0
LAD beyond −30°	87	0·7	71	0·8
Complete BBB (R and L)	59	0·4	35	0·4
Proven coronary disease	21	0·2	14	0·2
Heart block	16	0·1	14	0·2
WPW	15	0·1	12	0·1
Viral myocarditis	9	0·1	2	0
'Miscellaneous'	79	0·6	63	0·8
Normal	12 253	92·2	7761	90·0
Total	13 294	100·0	8625	100·0

RBBB, right bundle-branch block; LAD, left axis deviation; WPW, Wolff-Parkinson-White syndrome.

datory requirement in pilots and personnel of allied occupations such as air traffic control officers (ATCO). Abnormalities of repolarisation are the commonest anomalies and the recent Bethesda conference on 'Cardiovascular problems associated with aviation safety' (American College of Cardiology, 1975) highlights current concern and controversy about interpretation and management.

In the 4 years 1972 to 1975 13 294 routine electrocardiograms were carried out on 8625 individual RAF aircrew. A crude breakdown is shown in Table 1 from which it will be seen that 416 electrocardiograms on 338 of the men showed repolarisation changes at rest, that is 3·1 per cent of all the electrocardiograms and 3·9 per cent of the men had ST-T changes constituting 40 per cent of all the recorded abnormalities. It was particularly apparent that a considerable number of these were in young asymptomatic individuals who seemed unlikely to have significant coronary heart disease, cardiomyopathy, or other important disease. Of electrocardiograms recorded from 5217 civil professional aircrew and ATCOs between September 1974 and December 1975, 202 (3·9%) showed ST-T abnormalities (Joy, 1977).

T and ST abnormalities in the apparent absence of disease are well known to occur and have been variously attributed to a wide variety of causes including emotion (Taggart *et al.*, 1978), neurocirculatory asthenia (Holmgren *et al.*, 1959), the hyperkinetic heart syndrome (Guazzi *et al.*, 1975), posture (Mayerson and Davis, 1942), and hyperventilation (Kemp and Ellestad, 1968).

Our previous studies on the effects of emotions of different types and intensities including driving in city traffic (Taggart *et al.*, 1969), speaking before an audience (Taggart *et al.*, 1973), racing car driving (Taggart *et al.*, 1969), and parachute jumping (Taggart *et al.*, 1974) have shown an increased plasma catecholamine concentration associated with ST-T changes in young, fit adults, suggesting a possible cause and effect relation. This contention receives support from observations showing that beta-blockade may prevent or at least minimise such electrocardiographic abnormalities in response to emotion (Taggart *et al.*, 1973), the hyperkinetic heart syndrome (Guazzi *et al.*, 1975), posture (Kattus *et al.*, 1970), and hyperventilation (Furberg and Tengblad, 1966). However probable that such changes are caused by variations in autonomic activity/response, nevertheless their similarity to those associated with myocardial ischaemia remains irrefutable.

Maximal treadmill exercise testing rather than clarifying may, in some patients, compound the problem. Though achieving a 60 to 70 per cent sensitivity, this test suffers the important limitations imposed by its roughly 90 per cent specificity.

Consequently the state of the coronary arteries has often to be decided by coronary arteriography. Though the demonstration of normal coronary arteries is sufficient to satisfy certain licensing bodies (American College of Cardiology, 1975), uncertainties as to prognosis remain in view of the lack of understanding of the pathophysiology involved. For this reason, in the course of routine investigation of such patients we have included observations on intravenous infusion of adrenaline and noradrenaline with and without beta-adrenergic blockade.

We present now observations on 20 asymptomatic men referred consecutively for investigation of T and ST abnormalities and whose licence or livelihood was jeopardised. All had normal coronary arteriograms except a 55-year-old man with an isolated 50 per cent lesion of the left anterior descending coronary artery.

Subjects and methods

Studies were made of 20 male subjects aged 18 to 55 (mean 34). Of these, 10 were qualified pilots of varying experience, 3 were applicants for training, 2 were air traffic control officers, 2 were army ground personnel, 1 was an air commodore, 1 was an RAF navigator, and 1 was an RAF air engineer who wished to become a flight engineer. All were asymptomatic and physical examination disclosed nothing more than mild hypertension in 4 for which one (case 18) had been taking chlorthalidone. Nine were regularly engaged in athletic activities which in 4 were of exceptional standard. Eighteen had been referred because of an abnormal routine resting electrocardiogram. Two had previous nonspecific symptoms at which time an abnormal electrocardiogram had been recorded; one of these persons is considered in detail (see below). The purpose of the observations was explained in detail to each subject.

EXERCISE TESTING

Maximal treadmill exercise tests were conducted using the multi-stage procedure derived by Doan *et al.* (1965). The end point chosen was the subject's limit of tolerance rather than target heart rates. The three-channel Avionics monitor model 3000 and computer programmer P.100 was used with the CM lead system. The 3 praecordial leads were positioned after inspection of the resting electrocardiograms of each subject in order to include those areas where maximum changes had been observed. CM5 was incorporated in each case.

Each subject underwent at least 2 tests, the first conducted without prior medication and the second after an oral dose of 80 mg oxprenolol (Trasicor) administered 1½ hours previously. The following procedure was adopted. After 5 minutes of recumbent rest a blood sample was taken for plasma catecholamine estimations. Electrocardiograms were then made in the lying and standing position, during 20 seconds of hyperventilation, during the performance of the Valsalva manoeuvre, at the end of each stage of exercise, and at 1-minute intervals for 10 minutes in the recovery period monitored with the subject recumbent. A second blood sample for catecholamine estimations was taken in the recumbent position immediately on completion of exercise. Cuff blood pressure measurements were made at rest before exercise, 30 seconds before the end of each stage, and at minute intervals during the 10-minute period of recovery. In no instance was it necessary to terminate the test prematurely.

Tests were considered positive when ST segment depression of 1 mm or more, as compared with the control tracing, was observed in at least 6 consecutive beats, measured at 60 milliseconds after the nadir of the S wave with reference to the PR segment and irrespective of whether the ST segment was upsloping, horizontal, or downsloping. Inevitably when eyeballing analysis is employed there is a 'grey area of indecision' and such tests were classified as 'borderline'.

BETA-BLOCKADE

An oral dose of propranolol (20 to 40 mg) was given to 10 subjects outside hospital immediately after recording an abnormal electrocardiogram, and the tracing was repeated 1 to 2 hours later.

ECHOCARDIOGRAMS

Echocardiographic studies were carried out in all subjects in the supine position using a commercially available Echograph (Smith-Kline Ekoline 20A) and a 2·25 MHz transducer focused at 7·5 cm and recording on a Cambridge strip chart recorder.

Mitral valve echoes were identified by placing the transducer in the 3rd, 4th, or 5th intercostal space and directing the beam posteriorly or slightly medially. Aortic valve echoes were obtained by rotating the transducer medially and cephalad from the mitral valve position.

Interventricular septal echoes were recorded at two levels, that is at the mitral level (position 3) and at the submitral level when the ultrasonic beam was passing through the left ventricular cavity just past the tip of the mitral valve.

Free posterior left ventricular wall echoes were recorded at the submitral level (position 4) and measured in end-diastole.

Interventricular septal to posterior free ventricular wall thickness ratio was calculated and considered abnormal when exceeding 1·5.

The left ventricular outflow tract width was measured at the mitral level (position 3) as the minimum distance between the closed position of the mitral valve (point 5) and the left side of the interventricular septum at the onset of systole.

In the mitral valve echograms we studied the behaviour of the mitral apparatus in systole; when the systolic anterior motion (SAM) was equivocal, incomplete, small, or inconstant, simple provocative tests using amyl nitrite inhalation were performed. We found the Valsalva manoeuvre of no help as a provocative test as it destroyed the quality of the echoes.

Aortic valve echoes were studied in particular for the character of cusp motion pattern and for evidence of mid-systolic closure.

CARDIAC CATHETERISATION

Left heart catheterisation and coronary arteriography using the Sones technique was carried out in all patients. Single plane left ventricular cineangiography was performed in the right anterior oblique position (RAO) at 30° at 40 frames per second. Right heart catheterisation was also undertaken in 10 patients. Ejection fractions were calculated using the method of Sandler and Dodge (1968) modified for the right anterior oblique position.

INFUSION OF CATECHOLAMINES

Each subject received separate intravenous infusions of adrenaline, and then, after a half-hour interval, noradrenaline without any prior medication. The same infusion procedure was repeated 1½ hours after the oral administration of 80 mg oxprenolol. Dilutions of adrenaline and noradrenaline were prepared in normal saline within 1 hour of the start of each infusion. The Harvard constant infusion pump (model 975) was used. Electrocardiograms were recorded on a three-channel Mingograph, the lead positions being selected as for the exercise tests.

A procedure was devised whereby each infusion included 4 different rates: 0·024 μg/kg per min, 0·047 μg/kg per min, 0·091 μg/kg per min, and 0·18 μg/kg per min. Each infusion was continued for 4 minutes with an interval of 3 minutes or longer as necessary for the blood pressure to return to its control value. The procedure was terminated prematurely if subjective symptoms appeared or the blood pressure increased to more than 200 mmHg systolic or 120 mmHg diastolic. A dummy run was contrived in 6 subjects (4 group 1 and 2 group 2) by adjusting the pump to appear to be infusing but in fact not doing so.

In 5 subjects noradrenaline infusion was repeated after administration of atropine 1·2 mg in order to assess whether baroreceptor reflex effects were relevant.

PLASMA CATECHOLAMINE ESTIMATIONS

Venous blood samples were collected for plasma catecholamine estimations immediately before exercise and at maximum exercise on both the tests with and without beta-blockade. Samples were processed and analysed by methods previously described (Carruthers *et al.*, 1970).

STATISTICAL ANALYSIS

Plasma catecholamine concentrations being positively skewed, non-parametric statistics were employed. The Mann-Whitney U test was used to test the significance of the difference between medians of unpaired populations and the Wilcoxon signed rank test for paired populations.

Mean values with Student's t test were used for the other measurements.

Results

RESTING ELECTROCARDIOGRAM

Three electrocardiographic patterns, typical of those in the present study, are shown in Fig. 1. Low amplitude, flat, or inverted T waves in the inferolateral leads (type 1) were present in 13 subjects, T inversion confined to the septal leads was present in 4 (type 2), and ST segment depression (type 3) in 3.

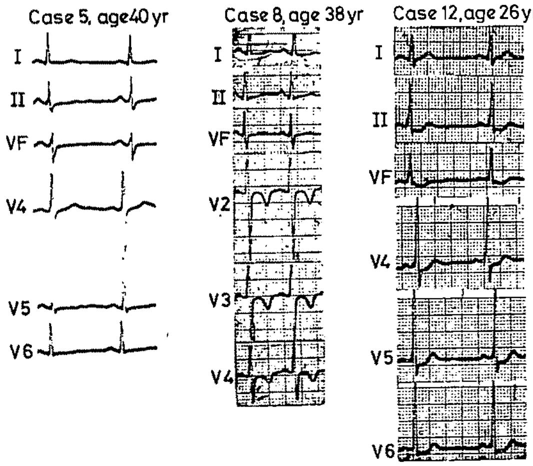

Fig. 1 *Three typical electrocardiographic patterns designated for simplicity of discussion as type 1 (left), type 2 (centre), and type 3 (right).*

POSTURAL VARIATION

Type 1 changes were more obvious when the subject was standing than when lying (Fig. 2). This postural effect was abolished by an oral dose of 80 mg oxprenolol. Type 2 and 3 changes were uninfluenced by body position.

REST AND TRANQUILLITY

Type 1 pattern was normalised either by an overnight rest in hospital or by beta-blockade in 9 and partially so in 4 (Fig. 3), types 2 and 3 retaining their 'abnormal' configuration.

BETA-BLOCKADE

After beta-blockade outside hospital, 7 type 1 subjects all reverted to normal whereas 2 type 2 and 1 type 3 were unchanged.

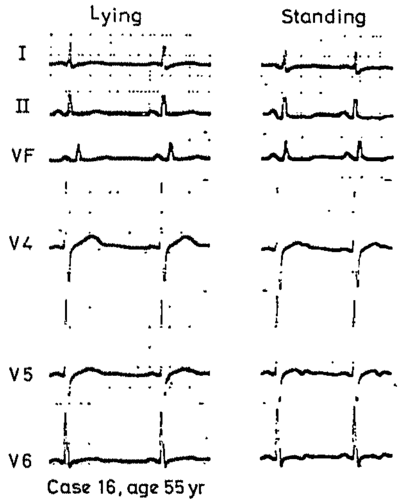

Fig. 2 *Electrocardiographic abnormalities more obvious in the erect position in type 1.*

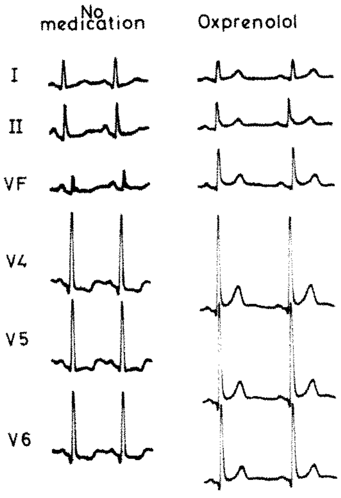

Fig. 3 *Electrocardiographic abnormalities normalised by either an overnight rest or beta-blockade.*

HYPERVENTILATION AND VALSALVA

Forced hyperventilation and the Valsalva manoeuvre produced variable and inconsistent effects.

VACILLATION

A feature of type 1 was a tendency to vacillate between upright and inverted T waves. Electrocardiograms of a 39-year-old flight lieutenant (case 9) between the years of 1961 and 1975 are illustrated in Fig. 4. Four definite periods of T wave abnormality were apparent, with intervening times when the T waves were normal. Two weeks before the first abnormal electrocardiogram he had a febrile illness, and the T wave abnormalities were attributed to viral myocarditis, and subsequent periods of T wave inversion to recurrent attacks. He was asymptomatic throughout, an active sportsman with no abnormality on examination, chest *x*-ray, or biochemistry at any time, and was free of any coronary risk factors; the echocardiogram was normal.

ECHOCARDIOGRAMS

A septal to free posterior left ventricular wall ratio of greater than 1·5 was present in 3 subjects and of less than 1·5 in 17 (Table 2).

EXERCISE TEST

Maximum treadmill exercise tests without prior medication showed changes that would be classed as positive for myocardial ischaemia in 6, borderline in 5, and negative in 9 (Fig. 5). After oxprenolol, no test was positive, 3 were borderline, and 17 were negative (Fig. 6) (Table 2). Heart rates in the unblocked tests increased from a mean value of 73 (± 12·6 SD) at rest to 172 (± 15·5) at maximum exercise and in the blocked tests from 64 (± 8·2) at rest to 119 (± 21·1) at maximum exercise. Heart rates were significantly lower in the blocked tests both at rest ($P < 0{\cdot}001$) and at maximum exercise ($P < 0{\cdot}001$). All but 3 subjects were unable to exercise for as long after oxprenolol. The mean times in minutes on the treadmill with and without medication, respectively, were 13·0 (± 2·5 SD) and 14·0 (± 3·3). This difference fails to reach significance at the 5 per cent level for the group as a whole.

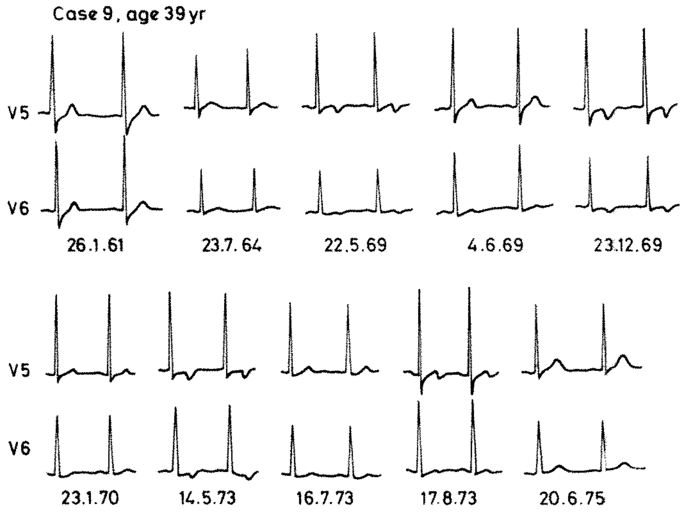

Fig. 4 *Tendency to vacillate between normal and abnormal pattern, illustrated by case 9, aged 39. His age was 24 in 1961.*

Table 2 *Individual data on 20 subjects in study*

Case no.	*Age*	*ECG type*	*Echocardiograms*			*Treadmill exercise**		*Cardiac catheterisation†*		
			IVS (mm)	*PLVW (mm)*	*Ratio (IVS/PLVW)*	*No medication*	*Oxprenolol*	*RHC*	*LVEDP*	*EF*
1	23	1	11	9	1·22	–	–	+	12	0·73
2	29	1	10	9	1·11	–	–	+	3	0·59
3	30	1				–	–	–	10	0·66
4	38	2	14	8	1·75	+	–	+	12	0·76
5	40	1				–	–	+	11	0·75
6	26	2	9	9	1·0	B	–	+	9	0·78
7	38	1	10	9	1·11	–	–	+	10	0·69
8	38	2	14	9	1·55	–	–	+	12	0·68
9	39	1	12	9	1·33	B	B	–	15	0·77
10	23	1	9	8	1·12	+	–	+	11	0·82
11	21	1	8	8	1·0	–	–	–	7	0·95
12	26	3	9	8	1·12	+	–	+	10	0·72
13	32	1	11	9	1·22	B	B	–	9	0·72
14	48	3	9	9	1·0	+	B	–	16	0·62
15	35	2	9	8	1·12	–	–	–	5	0·71
16	55	1	10	10	1·0	+	–	+	7	0·89
17	41	1	18	9	2·0	B	–	–	5	0·75
18	53	3	10	9	1·11	+	–	+	15	0·83
19	43	1	10	8	1·25	B	–	–	5	0·84
20	18	1	8	8	1·0	–	–	–	8	0·59

IVS, intraventricular septal thickness; PLVW, posterior left ventricular wall thickness; * Treadmill tests: + a positive test; – a negative test; B, borderline result.

† Cardiac catheterisation: RHC, right heart catheter, designated + or – to indicate whether included or not. LVEDP, left ventricular end-diastolic pressure; EF, ejection fraction.

No subject developed arrhythmia in any tests. Blood pressure response during and after the tests was normal in all subjects and did not suggest any impairment of left ventricular function.

CARDIAC CATHETERISATION

Of 20 subjects, 3 had a left ventricular end-diastolic pressure (LVEDP) above 12 mmHg and an additional 3 showed raised values after left ventricular cineangiography. Right-sided pressures were normal in all 10 subjects in whom they were measured (Table 2).

Coronary arteriography was normal in all subjects except one (case 16) who had an isolated 50 per cent stenosis of the left anterior descending coronary artery. One other had an anomalous origin of a small circumflex vessel from the right coronary artery.

Mean left ventricular ejection fraction (LVEF) was 0·74 (± 0·09 SD). In 12 subjects LVEF was in the normal range of 0·59 to 0·75 and in 8 it was increased, ranging from 0·76 to 0·95 (Table 2).

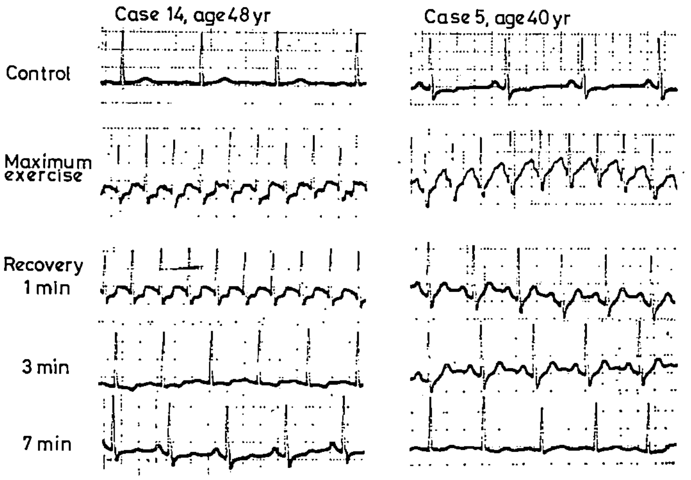

Fig. 5 *Examples of a positive (left) and negative (right) maximum treadmill exercise test in different subjects without medication.*

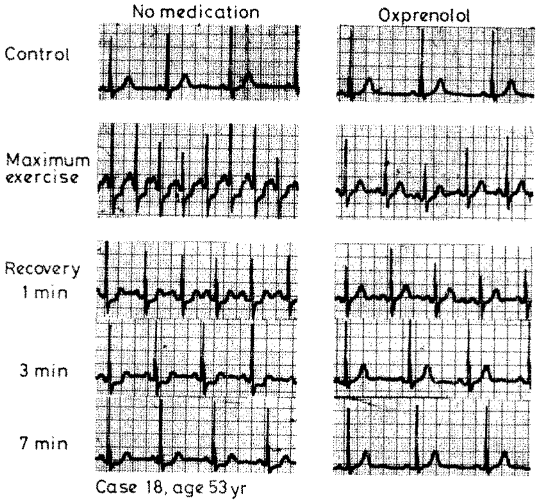

Fig. 6 *Case 18, age 53—illustrating a positive maximum treadmill test (left) without medication and a negative test (right) after 80 mg oxprenolol.*

INFUSION STUDIES

Adrenaline

In subjects with type 1 changes on the resting electrocardiogram, in whom an overnight rest in hospital resulted in normalisation of the electrocardiogram, intravenous adrenaline infusion reproduced these abnormalities. The configuration of the reproduced changes was similar to the original abnormal pattern (Fig. 7). The tendency of this group to vacillate between normal and abnormal has been mentioned, and in those in whom a sufficient number of good quality previous electrocardiograms was available, the intermediary patterns were seen to be mimicked by the evolutionary changes induced by adrenaline.

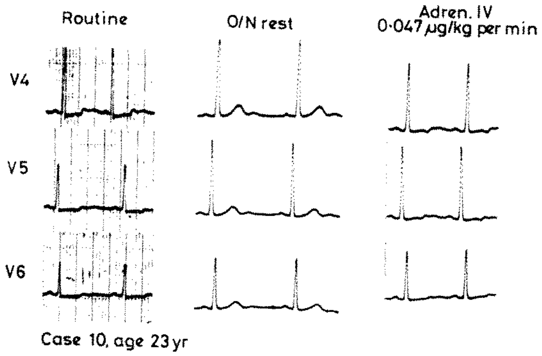

Fig. 7 *Abnormal electrocardiographic pattern reproduced by intravenous infusion of adrenaline in case 1, age 23, whose electrocardiogram had become normalised by an overnight rest.*

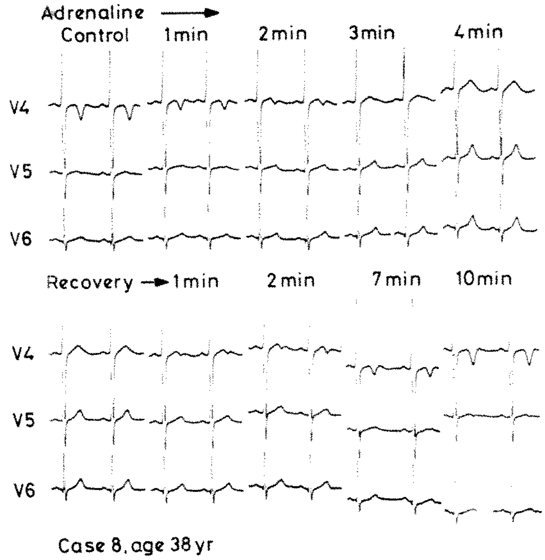

Fig. 8 *Normalisation of electrocardiogram by intravenous adrenaline in case 8, age 38, in whom an overnight rest did not correct the electrocardiogram, showing an effect opposite to that illustrated in Fig. 7.*

In subjects with type 2 changes in the resting electrocardiogram, in whom an overnight rest did not result in normalisation, intravenous adrenaline did so (Fig. 8), having seemingly the opposite effect to that seen in type 1.

Neither the process of setting up the infusion nor the dummy run incorporated in 6 subjects (4 type 1 and 2 type 2) influenced the ST-T configuration.

In the 3 subjects with type 3 changes intravenous adrenaline appeared to be without effect on the ST segment or T wave.

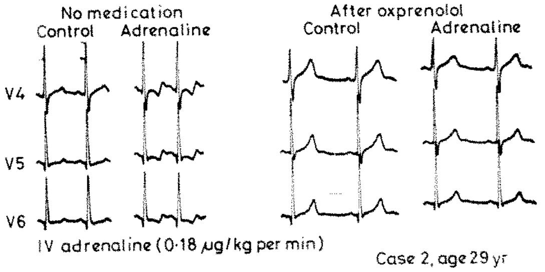

Fig. 9 *Effect of intravenous adrenaline on electrocardiogram prevented by prior administration of oxprenolol.*

Adrenaline after beta-blockade

Adrenaline infusion when repeated using the identical procedure but performed 1½ hours after oxprenolol was completely without effect on the ST-T segment in all subjects (Fig. 9).

Noradrenaline after beta-blockade

Noradrenaline administered using the same dosage scheme was without influence on the electrocardiogram except for the predictable bradycardia associated with an increase in blood pressure.

A repeat infusion of noradrenaline after beta-blockade again did not influence the ST-T segment.

Noradrenaline after atropine

In the 5 subjects (3 type 1, 2 type 2) who received a repeat infusion of noradrenaline after intravenous atropine but without prior beta-blockade, no effect was observed on the electrocardiogram except for some degree of tachycardia.

Plasma catecholamine concentrations

Plasma catecholamine concentrations immediately before and at cessation of treadmill exercise testing are presented in Table 3A and confidence limits in Table 3B. Values for total catecholamines, noradrenaline, and adrenaline obtained before exercise did not differ significantly from control subjects from whom samples were taken in tranquil conditions (Taggart, 1976). Both adrenaline and noradrenaline concentrations were increased at maximum exercise, these increases being comparable in both the tests with and without oxprenolol. There was no significant difference at the 95 per cent level between any of the respective unblocked and blocked values. Three individuals (2 type 1 and 1 type 3) showed exceptionally high noradrenaline concentrations in their post-exercise samples on both occasions.

Table 3A *Median plasma catecholamine concentrations (μg/l) immediately before and at cessation of exercise in 20 subjects tested without prior medication (left) and after oxprenolol (right) (P derived by Wilcoxon signed rank test)*

		No medication		*Oxprenolol*	
Total catecholamines	Before	0·8	$P < 0{\cdot}01$	0·8	$P < 0{\cdot}01$
	After	1·8		1·95	
Noradrenaline	Before	0·6	$P < 0{\cdot}01$	0·55	$P < 0{\cdot}01$
	After	1·35		1·6	
Adrenaline	Before	0·1	$P < 0{\cdot}01$	0·2	$P < 0{\cdot}01$
	After	0·4		0·4	

Table 3B *Confidence limits for median values in* Table 3A

No medication	*Oxprenolol*
$P(0{\cdot}6 < 0{\cdot}8 < 1{\cdot}2) = 99{\cdot}74$	$P(0{\cdot}6 < 0{\cdot}8 < 1{\cdot}3) = 99{\cdot}74$
$P(1{\cdot}0 < 1{\cdot}8 < 3{\cdot}2) = 99{\cdot}74$	$P(1{\cdot}0 < 1{\cdot}95 < 2{\cdot}9) = 99{\cdot}74$
$P(0{\cdot}4 < 0{\cdot}6 < 0{\cdot}9) = 99{\cdot}74$	$P(0{\cdot}3 < 0{\cdot}55 < 0{\cdot}9) = 99{\cdot}74$
$P(0{\cdot}6 < 1{\cdot}35 < 2{\cdot}8) = 99{\cdot}74$	$P(0{\cdot}6 < 1{\cdot}6 < 2{\cdot}5) = 99{\cdot}74$
$P(0{\cdot}1 < 0{\cdot}1 < 0{\cdot}4) = 99{\cdot}74$	$P(0{\cdot}1 < 0{\cdot}2 < 0{\cdot}4) = 99{\cdot}74$
$P(0{\cdot}1 < 0{\cdot}4 < 0{\cdot}5) = 99{\cdot}74$	$P(0{\cdot}1 < 0{\cdot}4 < 0{\cdot}7) = 99{\cdot}74$

Discussion

The diverse nature of the T wave changes depicted in this study poses the question as to whether they represent totally unrelated pathological entities or merely an altered and variable physiological response. We would prefer the latter alternative since the T changes may be linked together if we postulate a bimodal response to adrenaline. Our data may be conveniently represented according to the model in Fig. 10 whereby the T wave is upright above a horizontal line, inverted below it, and adrenaline drives the curve to the right.

Testing this hypothesis, we may propose that those persons designated as having type 1 electrocardiographic abnormalities (Fig. 1) occupy position 1 (Fig. 10) when in a tranquil state. Any anxiety, such as that attendant on a medical examination, particularly if a licence and professional livelihood may be jeopardised, would be expected to move the electrocardiogram towards position 2. Either the tranquillity of an overnight rest or beta-blockade would return the electrocardiogram to position 1. The tendency to vacillation (Fig. 4) between upright and inverted T waves so characteristic of type 1 changes is easy to understand on this basis. The fact that they become more obvious in the erect position (Fig. 2) may be because of increased sympathetic

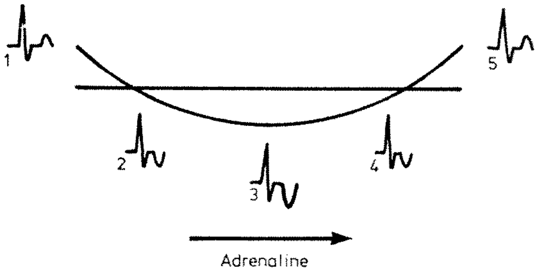

Fig. 10 *Diagrammatic illustration of the bimodal response to adrenaline apparent from the data in this study.*

tone (Nordenfeld, 1965). Again, infusion of even a low dose of adrenaline after an overnight rest moves the electrocardiogram pattern from position 1 to 2 and this effect may be prevented by previous beta-adrenergic blockade.

Those whose resting electrocardiograms occupy position 3 (type 2) would be unlikely to return to normal by tranquillity or beta-blockade as it would require the curve to be driven too far to the left. The small sympathetic discharge induced by posture would be insufficient to produce much, if any, discernible effect. Infusion of adrenaline, however, in a higher dosage should drive the curve to the right resulting in normalisation of the electrocardiogram at position 5 and subsequent return of the 'abnormal' pattern on recovery (Fig. 9). This effect should be prevented by beta-blockade, as was the case in our studies.

An unavoidable weakness of this study is the lack of control subjects. For obvious reasons it was considered inappropriate to conduct this series of tests in the absence of indisputable clinical indications. Lepeschkin *et al.* (1960) reported the effect of adrenaline and noradrenaline infusion on the electrocardiogram of 100 subjects with no clinically apparent heart disease, though coronary arteriography was not performed. Adrenaline infusion in doses 0·2 and 0·3 μg/kg per min produced T inversion in the lateral praecordial leads in only 4 of 60 young women (5·7%), 33 of whom were pregnant, and infusion of 0·1 μg/kg per min produced similar changes in only 2 of 40 (5%) young men, 20 of whom were active athletes. This contrasts with the present study in which T inversion was produced in all 13 subjects with type 1 resting electrocardiographic abnormalities in whom infusion was started with a normal T wave, in response to an infusion for similar length of time of up to 0·18 μg/kg per min. The 3 subjects with ST depression in their resting electrocardiogram at no time had T wave inversion in routine recordings and the T wave was uninfluenced by adrenaline.

Noradrenaline infusion resulted in a decrease in heart rate and either little change in, or a tendency to increase T wave amplitude, and was similar to the findings of Lepeschkin *et al.* (1960). The latter workers, however, attributed the difference between adrenaline and noradrenaline to reflex vagal excitation and sympathetic inhibition since after atropine noradrenaline behaved more like adrenaline. Other workers have reported the same phenomenon both in intact man (Littman *et al.*, 1950) and in the isolated animal heart (Johansson and Vendsalu, 1957). In our studies the effect of noradrenaline was uninfluenced by atropine in the 5 subjects in whom this was included suggesting that the difference between the two hormones is at cellular level. That such a difference exists is supported by some animal studies (Giotti *et al.*, 1973) and contradicted by others (Sparks *et al.*, 1970).

It is appropriate to consider to what extent the diagrammatic representation of our data (Fig. 10) may be explained in physiological terms.

Bayliss and Starling (1892) first showed that the mammalian T wave might be attributed to differences in the duration of electrical excitation in different parts of the ventricle, and early work in this field (see Adrian *et al.*, 1976, for references) strongly supported this view. The original arguments are carefully summarised by Mines (1913).

Subsequent argument has largely concerned the location of the relevant gradients of action potential duration and the cellular mechanism by which this gradient is generated. In isolated pieces of sheep ventricle, Cohen *et al.* (1976) showed that a duration gradient appears, as a consequence of repetitive activity, between tissue taken from the base of the septum and the epicardial surface of the apex. These experiments do not, however, distinguish between whether the gradient occurs between subepicardium and subendocardium (Gardberg and Rosen, 1957), between base and apex, or a number of other possibilities. Recent experiments by Kuo and Surawicz (1976) show that not all T wave changes are associated with changes in endocardial/epicardial gradients. They showed that reversal of T wave polarity was, however, associated with changes in the difference between monophasic action potentials on the anterior and posterior ventricular walls.

In Fig. 11 and 12, we have labelled the two regions responsible for the duration difference relevant to the T wave as area 1 (for example, endocardial septum) and area 2 (for example, epicardial apex) to avoid possible confusion with particular models of the T wave. Their normal time relation to each other and to the electrocardiogram is shown in Fig. 11 (left). Any physiological event that causes area 2 to repolarise later than area 1 causes inversion of the T wave (Fig. 11—centre).

The bimodal response to adrenaline proposed in Fig. 10 is illustrated in Fig. 11 in terms of action potential duration. In this instance it is assumed that whereas both action potentials (APs) are lengthened progressively there is an initial greater lengthening of area 2 action potential duration and subsequently a greater lengthening of area 1 action potential duration. There is conflicting evidence as to whether adrenaline shortens or lengthens the action potential duration. Under different conditions, catecholamines may do either (Giotti *et al.*, 1973). However, whichever alternative is the case is immaterial. Hypothesis I supposes that adrenaline causes a

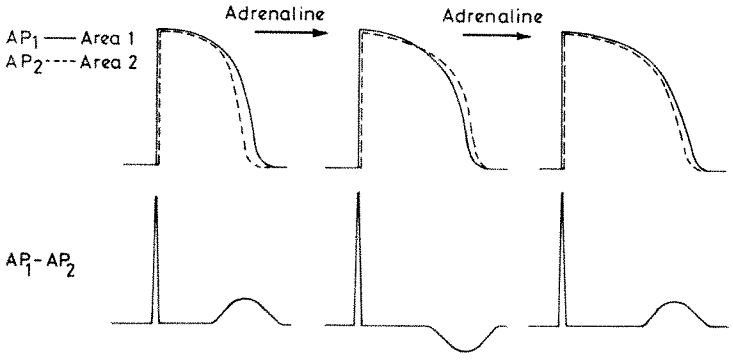

Fig. 11 *Theoretical relation of action potentials of area 1 and area 2 (above) and the praecordial electrocardiogram (below). The bimodal electrocardiographic response to adrenaline by differential rates of change of action potential duration.*

lengthening of both action potential groups but area 2 has a greater initial response but less ability to sustain it. Hypothesis II supposes that adrenaline causes a shortening of both action potential groups and that in this instance area 1 has a greater initial response but less ability to maintain it. By either of these means a unimodal change of action potential duration would result in a bimodal T wave response to adrenaline. In this context it is interesting to note that Kuo and Surawicz (1976) have recently compared changes occurring after left stellate ganglion transection with those after right stellate ganglion stimulation. These procedures produced similar changes in T wave polarity despite the fact that the former *prolonged* and the latter *shortened* the QT interval.

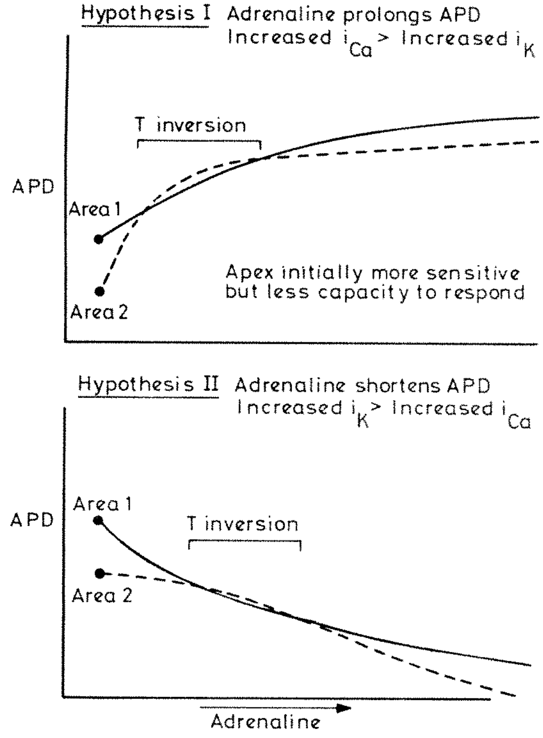

Fig. 12 *Two hypotheses allowing a bimodal T wave response irrespective of whether adrenaline results in lengthening or shortening of action potential duration.*

Whatever the precise physiological mechanisms involved there is undoubtedly an unusual beta-receptor responsiveness. It was to have been expected, therefore, that an incidence of false positive tests in excess of 10 per cent would be encountered in the subjects under discussion since a high incidence has been reported in people with normal coronary arteriograms and neurocirculatory asthenia (Murai, 1960), hyperventilation (Jacobs *et al.*, 1974), and pronounced orthostatic changes (Kattus *et al.*, 1970). All these are situations in which it has been suggested that an altered autonomic response is involved (Nordenfeld, 1965; Friesinger *et al.*, 1972), a contention that receives support from the patients of Kattus *et al.* whose false positive tests were normalised after beta-blockade.

Reversal of functional electrocardiographic abnormalities by oral propranolol administered as a single dose (Noskowicz and Chrzanowski, 1968) or as a day course (Jackson, 1971) has been described. Coronary arteriograms were not performed on these patients. Considering the question as to whether beta-blockade may be useful as a test to differentiate functional from organic ST-T changes, Jackson points out that whereas organic ST changes were improved with propranolol they nevertheless remained abnormal. Furberg (1967) reviewing conflicting evidence concluded that ST-T changes associated with organic disease were not significantly altered by propranolol. The results of Prichard and Gillam (1971) accord more closely with Jackson (1971).

In certain persons, an electrocardiogram bearing a strong resemblance to myocardial ischaemia does not necessarily point to that diagnosis. Hence since they are not at hazard they should not have restrictions imposed upon them. However in pilots in whom sudden incapacitation may be disastrous, it would be premature to allow the issue or renewal of a licence in the presence of an abnormal electrocardiogram without coronary arteriography.

In the presence of unobstructed coronary arteries echocardiograms should be performed in order to detect 'silent' prolapsed mitral valve and asymmetric septal hypertrophy, since both are rare but real causes of collapse or sudden death. It seems hopeful that further studies along the lines of those presented here may facilitate the identification of this syndrome with sufficient clarity and confidence in order to rely on less invasive methods.

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Early clinical experience with the Hancock porcine xenograft valve prosthesis

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SUMMARY In a 2-year period, 75 Hancock porcine xenograft valves were inserted in 66 patients, 33 male and 33 female. Their average age was 55 years (range 14 to 69 years). The indication for operation was rheumatic heart disease (30 patients), prosthetic valve dysfunction (8 patients), papillary muscle dysfunction (8 patients), degenerative valve disease (13 patients), subacute bacterial endocarditis (3 patients), luetic valve disease (2 patients), congenital heart disease (1 patient), and traumatic valve damage (1 patient).

Forty-five valves were placed in the mitral, 28 in the aortic, and 2 in the tricuspid position; 9 patients required double valve replacement. Additional operative procedures included coronary artery vein bypass grafts (12 patients), tricuspid annuloplasty (6 patients), left ventricular aneurysmectomy (4 patients), open mitral valvotomy (3 patients), replacement of ascending aorta (1 patient), and closure of ventricular septal defect (1 patient). There were 2 hospital deaths (3%). Oral anticoagulation was continued for approximately 6 weeks postoperatively, when it was discontinued in all but 8 patients.

In the follow-up period—mean 16 months (range 8 to 31 months)—there were 4 late deaths, 2 of which were sudden. There was no documented episode of thromboembolism or valve degeneration. All except 2 patients were clinically improved from NYHA class III or IV preoperatively to class I or II postoperatively.

Initial results with Hancock porcine xenograft valves are most satisfactory and compare more than favourably with other commercially available valve substitutes.

The ideal heart valve substitute should be readily available, easily inserted, free from thromboembolic and infectious complications, haemodynamically satisfactory, and durable in the long term.

Dissatisfaction with the thrombogenicity, haemodynamic performance, and long-term durability of many mechanical prostheses (Stanford *et al.*, 1972; Vidne *et al.*, 1973) has led to the increasing use of many different types of tissue valves (Ionescu *et al.*, 1974; Wallace, 1975).

Of the tissue valves commercially available, the porcine aortic xenograft prepared by the 'stabilised glutaraldehyde process' and mounted on a flexible polypropylene Dacron-covered stent (Hancock Laboratories) has gained wide clinical acceptance. This valve was first used in Edinburgh in November 1973 and we report our initial clinical experience with it.

Subjects and methods

In a two-year period from November 1973, 75 Hancock valves were inserted into 66 consecutive patients at Edinburgh Royal Infirmary. There were 33 male and 33 female patients. The patients' ages ranged from 14 to 69 years (mean 55 years) (Fig. 1). Preoperatively, all patients were in class III or IV (New York Heart Association classification) (Fig. 2).

Forty-five valves were placed in the mitral position, 28 in the aortic, and 2 in the tricuspid position. Valve sizes ranged from between nos. 29 and 35 in the mitral position, nos. 21-29 in the aortic position, and no. 33 in the tricuspid position.

Of 57 single valve replacements, 36 patients had

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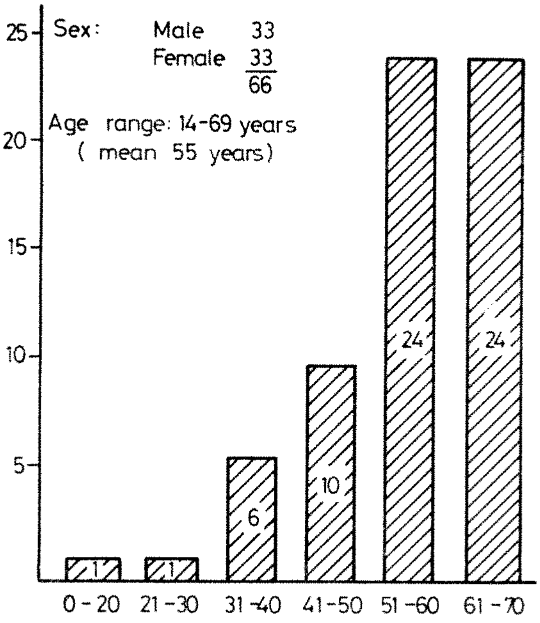

Fig. 1 *Age and sex of patients.*

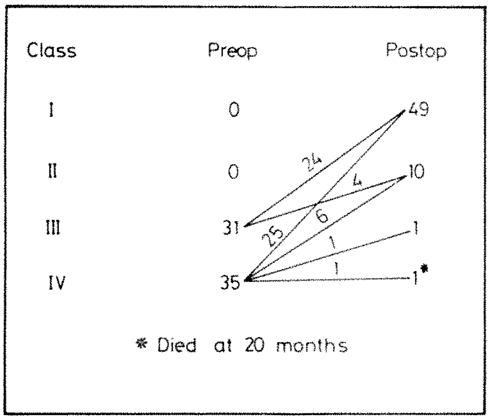

Fig. 2 *Symptomatic improvement (NYHA classification).*

mitral valve replacement and 21 aortic valve replacement.

Seven patients had double valve replacement (aortic and mitral) and 2 patients underwent mitral and tricuspid valve replacement (Table 1).

Additional procedures in 27 patients included 1 to 4 saphenous vein aortocoronary bypass grafts (12 patients), tricuspid annuloplasty (6 patients), resection of left ventricular aneurysm (4 patients), open mitral valvotomy (3 patients), replacement of the ascending aorta (1 patient), and closure of ventricular septal defect (1 patient).

In 53 patients in whom coronary artery disease was either excluded by selective coronary angiography or was not suspected, there was 1 death (mortality 1·9%) after a single aortic valve replacement (Table 2).

In 13 patients, the presence of ischaemic heart disease was proved preoperatively by selective coronary angiography and left ventricular angiography. In 12 of these patients, valve replacement was combined with coronary artery vein bypass grafting without mortality. One patient, submitted to aortic and mitral valve replacement and left ventricular aneurysmectomy without coronary artery grafting, died intraoperatively, giving a hospital mortality for this group of 7·7 per cent (Table 3).

The aetiology of the valvular disease in the different patient groups is shown in Tables 4, 5, 7, and 8.

Table 2 *Valve replacement in patients without ischaemic heart disease*

Mitral valve replacement	28
Aortic valve replacement	18*
Mitral + aortic valve replacement	5
Mitral + tricuspid valve replacement	2
Total	53
*Hospital death	1 (1·9%)
Additional procedures:	
Tricuspid annuloplasty	6
Mitral valvotomy	2
Replacement ascending aorta	1
Total	9

Table 1 *Valve replacement and prosthetic size*

	No. of patients	*Valve(s) replaced*
Single valve	57	MV 36; AV 21
Double valve	9	MV + AV 7; MV + TV 2
Total	66	

Valve replaced	*No. of patients*	*Prosthetic size (range)*
Mitral	45	Nos. 29-35
Aortic	28	Nos. 21-29
Tricuspid	2	No. 33
Total	75	

Table 3 *Valve replacement in patients with ischaemic heart disease*

Mitral valve replacement + coronary artery bypass graft	6
Aortic valve replacement + coronary artery bypass graft	2
Mitral valve replacement + coronary artery bypass graft + LV aneurysmectomy	1
Aortic valve replacement + coronary artery bypass graft + LV aneurysmectomy	1
Mitral valve + aortic valve replacement + coronary artery bypass graft	1
Mitral valve + aortic valve replacement + LV aneurysmectomy	1*
Mitral valve replacement + coronary artery bypass graft + LV aneurysmectomy + closure of VSD	1
Total	13
*Hospital death	1 (7·7%)

Table 4 *Aetiology of valve disease*

Rheumatic heart disease	30
Prosthetic valve dysfunction	8
Papillary muscle dysfunction	8
Degenerative valve disease	13
Subacute bacterial endocarditis	3
Luetic valve disease	2
Congenital heart disease	1
Traumatic valve damage	1
Total	66

Table 5 *Indications for mitral valve replacement*

Rheumatic heart disease	22
Prosthetic valve dysfunction	4
Papillary muscle fibrosis	1
Papillary muscle rupture	4
Ruptured chordae tendineae	4
Q fever endocarditis	1
Total	36
Hospital mortality 0	

Table 6 *Previous operations performed in 35 patients with rheumatic mitral valve disease*

Operation	*No. of patients*
Closed mitral valvotomy × 1	9
× 2	2
× 3	1
Closed mitral valvotomy + mitral valve replacement	2
Closed mitral valvotomy × 3 + mitral valve replacement	1
Closed mitral valvotomy + aortic valve replacement	1
Closed mitral and aortic valvotomy + mitral and aortic valve replacement	1
Mitral valve replacement	2
Replacement of mitral valve prosthesis	1
Total (32 operations)	20

Table 7 *Indications for aortic valve replacement*

Rheumatic heart disease	5*
Calcific aortic stenosis	11
Subacute bacterial endocarditis	2
Luetic valve disease	2
Traumatic valve rupture	1
Total	21
*Hospital mortality	1 (4·8%)

Table 8 *Indications for double valve replacement*

Rheumatic heart disease	3
Prosthetic valve dysfunction + rheumatic heart disease	3
Double prosthetic valve dysfunction	1
Marfan's syndrome	1
Calcific aortic stenosis + ischaemic mitral regurgitation	1*
Total	9
*Hospital mortality	1 (11·1%)

Of the 35 patients whose first presentation for cardiac surgery had been with rheumatic mitral valve disease, 20 had already been submitted to a variety of surgical procedures (Table 6).

SURGICAL TECHNIQUE

Standard bicaval-aortic route cardiopulmonary bypass, using a disposable bubble oxygenator and roller pump, was employed. Flow rates varied between 2 and 3·5 litres/min with a mean arterial pressure between 40 and 70 mmHg. Mild hypothermia down to 31 °C was reached in most patients.

All operations were performed through a vertical median sternotomy incision. The aorta was cross-clamped throughout the intracardiac procedures, the myocardium being protected by continuous irrigation with cold saline solution at 4°C. Horizontal mattress sutures were used to secure all valves and the struts of the mitral and tricuspid prostheses were orientated so as to produce minimal obstruction to ventricular outflow.

Oral anticoagulation with warfarin was started on the first postoperative day and was discontinued after 6 weeks, except in those patients with a previous history of an embolism, left atrial thrombus at operation, or a giant left atrium.

Results

There were 2 hospital deaths (mortality rate 3%). One patient with calcific aortic stenosis and mitral regurgitation with coronary artery disease did not have a preoperative left ventricular cineangiogram as the aortic valve could not be crossed. At operation

Table 9 *Late mortality*

Patient	*Operation*	*Survival (mth)*	*Cause of death*	*Valve histology*
1	Mitral valve replacement + coronary artery vein bypass graft × 4	2	Congestive cardiac failure; left atrial clot at necropsy	Normal
2	Replacement of aortic valve prosthesis + mitral valve replacement + tricuspid annuloplasty	3	Cause unknown	Normal
3	Mitral valve replacement	4	Congestive cardiac failure with gross cardiomegaly; left atrial clot at necropsy	Normal
4	Replacement of mitral valve prosthesis	20	Congestive cardiac failure with gross cardiomegaly; extensive myocardial fibrosis and left ventricle thrombus at necropsy	Normal

Table 10 *Long-term follow-up*

No. of patients	64
Period of follow-up	8 to 31 months (mean 16 months)
Total follow-up period	1026 months
Long-term anticoagulation	8 patients
Valve failure	0
Valve infection	0
Episodes of thromboembolism	1

he was found to have a large left ventricular aneurysm with mitral valve papillary muscle dysfunction. After left ventricular aneurysmectomy, aortic and mitral valve replacement, the operation was concluded without incident. He suddenly developed ventricular fibrillation after wound closure and could not be resuscitated. The second hospital death occurred in a 69-year-old man submitted to aortic valve replacement, and was the consequence of laceration of the subclavian artery during insertion of a central venous pressure monitoring line. He was reopened on several occasions for bleeding before the bleeding point was identified, had massive blood transfusion, and died after 24 days from multiple system failure.

During the mean follow-up period of 16 months (range 8 to 31), there were 4 late deaths at 2, 3, 4, and 20 months. All occurred in patients with a long preoperative history of heart disease and congestive cardiac failure.

Necropsy was carried out in all patients. In 2, thrombus was found in the left atrium and in a third, with myocardial fibrosis and gross cardiomegaly, thrombus was found in the left ventricle. No thrombus was found on the prosthetic valves which were macroscopically and microscopically normal in every case.

FOLLOW-UP

Sixty-four patients were discharged and followed up for a total of 1026 months or 16 months/patient (range 8 to 30 months). Long-term anticoagulation was continued after 6 weeks in only 8 patients. There was no incidence of valve failure or infection or of paraprosthetic leak. One patient had transient blindness of one eye during the first 6 weeks while still on anticoagulation, from which he fully recovered. No other known or suspected embolic episodes were experienced.

SYMPTOMATIC IMPROVEMENT

Of 31 patients in class III (NYHA classification) preoperatively, 3 died, 24 improved to class I, and 4 to class II. Thirty-five patients were class IV preoperatively; 25 improved to class I, 6 to class II, and 1 to class III. One patient remained in class IV until death at 20 months and 2 other patients died.

Actuarial survival curves show an overall survival rate of just under 80 per cent at 2½ years. Over this period, survival after mitral valve replacement was 80·2 per cent and survival for valve replacement in association with ischaemic heart disease was 84·6 per cent at 36 months. For double valve replacement survival was 85·7 per cent at 2 years, and for single aortic valve replacement survival was 94·5 per cent at 18 months.

Discussion

The results of this study confirm the findings of others (Ionescu *et al.*, 1972; Brown *et al.*, 1974; Carpentier *et al.*, 1974; Horowitz *et al.*, 1974; Stinson *et al.*, 1974; Zuhdi, 1974; Zuhdi *et al.*, 1974; Cohn *et al.*, 1975; Pipkin *et al.*, 1976) that the porcine aortic xenograft bioprosthesis (Hancock Laboratories) functions very well as a heart valve substitute in the mitral, aortic, and tricuspid position in man.

A particular feature in these patients was the rapid and smooth immediate postoperative recovery that the majority enjoyed and which was attributed to the very favourable haemodynamic characteristics of these valves. Improvement in at least two functional classes was seen in 98 per cent of the surviving patients. Failure to obtain symptomatic improvement was related in one patient to myocardial disease after 3 previous mitral valve procedures, and to non-cardiac causes in another patient with osteoarthritis.

Serious valve-related problems were extremely few. In particular, there was no incidence of valve failure or infection over the first 2½ years postoperatively and there was only one probable episode of systemic embolisation. This occurred during the first 6 postoperative weeks while the patient was still on oral anticoagulation, a time when the valve sewing ring is not yet endothelialised and when the risk of systemic embolisation is known to be highest with all prostheses.

After this first 6-week period, anticoagulation with its attendant morbidity and mortality (Stanford *et al.*, 1972; Cleland and Molloy, 1973; Vidne *et al.*, 1973) was avoided in the large majority of patients (87%). It is possible that thrombus formation in the left atrium may have had a part to play in the sudden death of 2 patients comparatively soon after their oral anticoagulation had been discontinued. Because of our experience with these patients, we are now inclined to keep most patients on long-term oral anticoagulation after mitral valve replacement with a Hancock prosthesis if they have more than moderate left atrial enlargement and are in atrial fibrillation, and particularly if there is clot in the left atrium at the time of operation.

The durability of these valves, with not one single valve failure occurring throughout the follow-up period, has been most encouraging and is in striking contrast to the experience with many other earlier forms of tissue valve prosthesis, where there has been a steady attrition rate from the early postoperative period (Wallace, 1975). This improved durability has been largely attributed to 2 factors. The use of a flexible stent has been shown to reduce stress at the cusp edges on closure up to 90 per cent (Reis *et al.*, 1971); secondly, the glutaraldehyde process used to 'tan' the valve is known to produce much more stable cross-linkage between the collagen fibres of the leaflets than has been achieved with previous preservation methods (Carpentier *et al.*, 1969).

In our opinion, the Hancock porcine xenograft prosthesis fulfils many of the characteristics of an ideal human valve substitute and compared more than favourably with other commercially available valve substitutes.

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Left ventricular ejection power in coronary artery disease during atrial pacing

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SUMMARY Peak and mean left ventricular ejection power were measured during atrial pacing in 6 normal subjects (group I), 6 patients with coronary artery disease without myocardial infarction (group IIa), and 10 patients with coronary artery disease after myocardial infarction (group IIb). Pacing rates were 80 and 120/min. Power was determined by computer analysis of pressure, volume, and time. Data were normalised by end-diastolic volume and left ventricular muscle mass.

Peak left ventricular ejection power normalised by end-diastolic volume in normal subjects increased from 53·4 to 68·2 mW/ml (+28%, $P < 0{\cdot}01$). No change was seen in group IIa and IIb. Peak and mean left ventricular ejection power normalised by end-diastolic volume values at a pacing rate of 120 min were significantly lower in group IIa and IIb than in normal subjects. Mean muscle mass in normal subjects was 179 g and in group IIa 216 g ($P < 0{\cdot}05$). Peak power normalised by muscle mass in normal subjects tended to increase at 120/min whereas in group IIa it declined by 26 per cent ($P < 0{\cdot}001$).

These data indicate that the energy output of the left ventricle at rest may be the same in patients with significant coronary artery disease as in normal subjects. Increasing the heart rate from 80 to 120/min in a normal myocardium augments power but in coronary artery disease it remains static or falls.

Left ventricular dynamics can be described in terms of pressure, volume, and time. Pressure analysis according to the principles of the force-velocity-length relation has been performed by numerous investigators (Brutsaert and Sonnenblick, 1973; Sonnenblick and Strobeck, 1977). This method has answered many questions about the contractile behaviour of the myocardium in health and disease. Nevertheless it is based upon theoretical assumptions derived from isolated muscle preparations, and the validity of data from the intact heart is limited. Furthermore, pressure analysis gives no direct information about the function of the ventricle as a pump. It has been shown in studies on ventricular volume that the ejection fraction and the velocity of circumferential fibre shortening have value in the detection of myocardial abnormality (Sonnenblick and Strobeck, 1977). However, these indices do not describe pump function adequately, whereas left ventricular power during ejection combines the time-dependent changes in ventricular pressure and volume, and in animals has been shown to be useful as an index of cardiac performance under various haemodynamic conditions (Stein and Sabbah, 1976a, b).

This study was undertaken to determine left ventricular power in normal subjects and in patients with coronary artery disease both at rest and under stress, using a computer programme for simultaneous analysis of pressure, volume, and time developed by the group.

Subjects and methods

PATIENTS

The study was performed in 22 patients referred to our department for diagnostic cardiac catheterisation. Twenty-one were male and one (case 5) female. Six of the subjects were considered normal by noninvasive techniques, haemodynamic measurements, and coronary arteriography (group I, mean age 38 ± 12 years). These were studied because of chest pain of undetermined origin. Sixteen patients had coronary artery disease as shown by coronary

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arteriography (group II, mean age 49 ± 6 years) and were potential candidates for coronary artery surgery. Six of these patients had no history of myocardial infarction (group IIa, mean age 46 ± 7 years); in the remaining 10, previous myocardial infarction had been clearly documented by electrocardiography and enzyme studies (group IIb, mean age 50 ± 5 years). Sinus rhythm with normal atrioventricular conduction was present in all subjects. Patients with significant hypertension, mitral valve regurgitation, or major left ventricular wall motion abnormalities were exluded from the study. There was no statistical difference in body surface area between the groups (mean 1·83 ± 0·11 m^2).

CARDIAC CATHETERISATION TECHNIQUES

Left and right heart catheterisation was performed in the fasting and recumbent state without premedication. Catheters were introduced under local anaesthesia using the Seldinger technique via the femoral vessels. Left ventricular and aortic pressures were measured simultaneously by catheter tip manometer[1] and a fluid filled catheter (multi purpose type[2]), respectively. In some instances a single catheter with two manometers was used.[1] The zero reference pressure was set at 5 cm below midchest level. Left ventricular angiography was performed by injection of 60 to 70 ml of 70 per cent Na-meglumine-iotalamate into the right atrium or pulmonary artery using a pigtail catheter[2]. With this technique premature ventricular contractions were completely avoided, and left ventricular volume remained unchanged throughout the period during which it was visible. This method has been described elsewhere in detail (Hagemann and Meyer, 1978). The ventriculograms obtained were of adequate quality for quantitative analysis by computerised videometry (Hagemann *et al.*, 1976). Only the earliest systoles providing adequate opacification of the left ventricular cavity were analysed.

The Judkins technique was used for coronary arteriography. Biplane cineangiography of the left ventricle was performed in the 30° RAO position. 35 mm film was used, exposed at 50 frames/second. A bipolar electrode catheter[3] inserted via a femoral vein was positioned against the wall of the right atrium. Effective pacing was obtained in all patients using pulses with an amplitude of 2·0 V and a duration of 1·0 ms. There were no complications from catheterisation.

PROCEDURE

All measurements were taken before coronary arteriography. After the catheters had been placed in position, atrial pacing was started at a rate of 80/min and continued for 3 minutes. Then left ventricular cineangiography was performed during atrial pacing. Left ventricular and aortic pressures were measured simultaneously, and the data stored on digital tape. After a recovery period of at least 20 minutes and when left ventricular systolic and end-diastolic pressures had returned to the control level the rate of pacing was increased to 120/min and continued for 3 minutes. When the new steady state was achieved cineangiography during atrial pacing was repeated, care being taken to ensure that the two ventriculograms were performed under the same conditions (amount of contrast medium, injection rate, *x*-ray factors, patient position, and position of tube and image intensifier).

DATA PROCESSING AND CALCULATIONS

Left ventricular and aortic pressures during cineangiography were calculated on line by a computer[1] sampling at 400 times a second. This computer programme has previously been described in detail (Jensch *et al.*, 1976). In addition, pressures, the electrocardiogram, and a frame exposure signal were recorded by a photographic recorder[2] running at 100 mm/s. Ventricular volume was determined at 20 ms intervals by videometry after video camera scanning of the 35 mm films. Single plane contour tracings were done by light pen. Volumes were calculated according to Simpson's rule using the same computer as for pressure calculations (interactive dialogue system). Volumes obtained by videometry were calibrated by a metal sphere of known volume which had been filmed in the same position as the left ventricle. No regression equations for correction of volumes were used. Smoothing and differentiation of the volume curve was performed as described by Savitzky and Golay (1964). Left ventricular muscle mass in end-diastole was calculated according to the modified method of Rackley *et al.* (1964). Muscle mass was not assessed in patients with infarction. In the angiographic method, wall thickness is assumed to be uniform, which is not true after myocardial infarction, and thinning over the necrotic area causes muscle mass to be overestimated by an unknown amount.

Simultaneous pressure and volume data during angiography were collated by the computer to establish a basic pressure volume progression. Using a linear interpolation procedure for the

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[1] Millar Instruments, Houston, Texas.
[2] Cordis Corporation, Miami, Florida.
[3] USCI, Glen Falls, New York.

[1] General Automation, Inc., Anaheim, Cal.
[2] Electronics for Medicine, Inc., White Plains, N.Y.

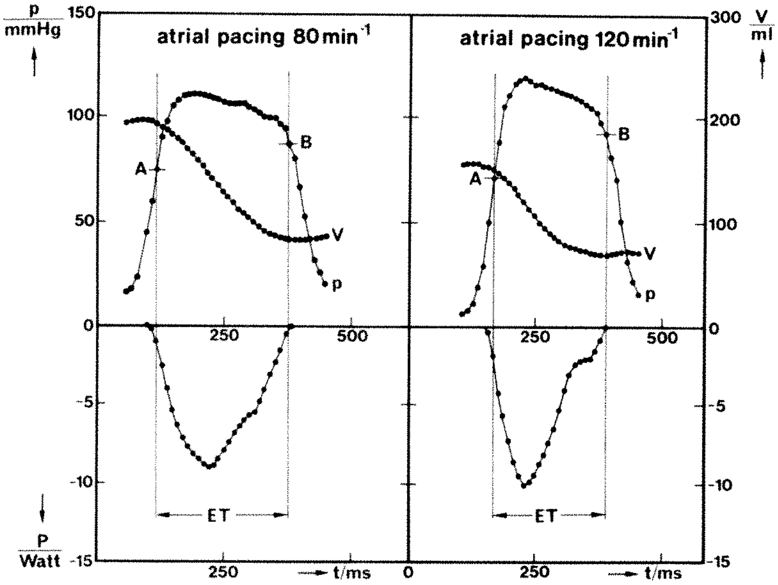

Fig. 1 *Left ventricular pressure, volume, and ejection power in a normal subject (case 4) during atrial pacing at a rate of 80/min* (left) *and 120/min* (right). *Abbreviations:* p = *pressure,* V = *volume,* P = *power,* ET = *ejection time,* t = *time,* A = *aortic valve opening,* B = *aortic valve closure. Power has been plotted on the negative* y *axis for mathematical reasons* $(-P = p \times (-dV/dt))$. *The negative sign has been neglected in the Tables and in the other Figures.*

volume curve calculations of instantaneous left ventricular power were made automatically at 10 ms intervals. By plotting power against time a continuous power curve was obtained (Fig. 1). Left ventricular power during ejection was calculated according to the equation

$$P = p \times dV/dt$$

where P = power, p = instantaneous left ventricular pressure, and dV/dt = instantaneous ejection blood flow. In SI units power is expressed in Watts. The conversion relation is

$$\text{power} = 1\ \text{mmHg} \times 1\ \text{ml} \times \text{s}^{-1} = 1{\cdot}333 \times 10^{-4}\ \text{Watt}.$$

The ejection time for calculation of mean power was identified from the aortic pressure tracing. The ejection fraction (%) was calculated as stroke volume/end-diastolic volume multiplied by 100.

STATISTICS

Statistical analysis was performed using the paired and unpaired t test (Ostle, 1963; Brownlee, 1965). A significant difference was accepted at a level of $\alpha = 5$ per cent ($P < 0{\cdot}05$).

Results

The data are summarised in detail in Tables 1 and 2.

END-DIASTOLIC VOLUME

The end-diastolic volume in group I at heart rates of 80 and 120/min was lower than in group II as a whole ($P < 0{\cdot}05$) and group IIb ($P < 0{\cdot}05$). No significant difference however was found between groups I and IIa. When the rate was changed from 80 to 120/min end-diastolic volume decreased in groups I and IIa by 19 per cent and in group IIb by 12 per cent.

EJECTION FRACTION

The ejection fraction at heart rates of 80 and 120/min in group II as a whole and group IIb was lower than in group I ($P < 0{\cdot}001$). At 80/min group IIa showed no significant difference compared with group I, but at 120/min the ejection fraction was significantly lower in group IIa ($P < 0{\cdot}02$). When the rate was increased the ejection fraction decreased in groups IIa and IIb by 17 per cent whereas no change occurred in group I.

PEAK AND MEAN EJECTION POWER

No statistical difference in these indices was found between normal subjects and patients in groups II, IIa, and IIb at heart rates of 80 and 120/min.

Table 1 *Haemodynamic data on normal subjects (group I)*

Case no.	*End-diastolic (volume ml)*		*Ejection fraction (%)*		*LV muscle mass (g)*		*Peak ejection power (mW)*		*Mean ejection power (mW)*		*Peak ejection power normalised by end-diastolic volume (mW/ml)*		*Mean ejection power normalised by end-diastolic volume (mW/ml)*		*Peak ejection power normalised by muscle mass (mW/g)*	
	a	*b*	*a*	*b*	*a*	*b*	*a*	*b*	*a*	*b*	*a*	*b*	*a*	*b*	*a*	*b*
1	162	126	72	69	198	—	10 929	9 352	5920	5870	67·5	74·2	32·5	39·2	55·2	47·2
2	160	136	55	50	197	—	8 812	7 806	4225	4382	55·0	81·0	23·2	32·0	44·7	39·6
3	172	153	65	48	189	—	6 652	7 951	4733	4495	38·7	52·0	26·1	23·4	35·2	42·0
4	198	156	58	57	170	—	9 066	10 233	5888	5404	45·8	65·6	25·9	30·5	53·3	60·2
5	124	92	64	67	132	—	5 537	5 504	4058	3558	74·3	64·4	28·9	34·7	41·9	41·7
6	172	134	56	58	185	—	6 772	9 627	5279	5192	39·3	72·0	30·3	38·9	36·6	52·0
Mean	164	133	62	58	179	—	7 961	8 412	5017	4817	53·4	68·2	27·8	33·1	44·5	47·1
± SD	± 24	± 23	± 7	± 9	± 25	—	± 1 988	± 1 715	± 809	± 833	± 14·9	± 9·9	± 3·4	± 5·9	± 8·3	± 7·8
P		< 0·001		NS		—		NS		NS		< 0·01		< 0·05		NS

a, b = atrial pacing 80 and 120/min, respectively.

The increase in heart rate did not significantly change peak and mean ejection power in group I and group IIb but in group IIa they decreased significantly by 25 and 18 per cent, respectively (both P < 0·001).

PEAK AND MEAN EJECTION POWER NORMALISED BY END-DIASTOLIC VOLUME

At 80/min there was no difference in peak power normalised by end-diastolic volume between normal subjects and those in groups II, IIa, and IIb.

Table 2 *Haemodynamic data on patients with coronary artery disease (group II, IIa, IIb)*

Case no.	*End-diastolic volume (ml)*		*Ejection fraction (%)*		*LV muscle mass (g)*		*Peak ejection power (mW)*		*Mean ejection power (mW)*		*Peak ejection power normalised by end-diastolic volume (mW/ml)*		*Mean ejection power normalised by end-diastolic volume (mW/ml)*		*Peak ejection power normalised by muscle mass (mW/g)*	
	a	*b*	*a*	*b*	*a*	*b*	*a*	*b*	*a*	*b*	*a*	*b*	*a*	*b*	*a*	*b*
Group IIa (no myocardial infarction)																
7	167	156	57	48	191	—	10 984	8 316	4657	4574	65·8	53·3	24·2	25·6	57·5	43·5
8	194	136	56	48	220	—	12 533	9 749	5303	3954	64·6	71·1	25·8	23·6	55·9	44·3
9	217	205	47	39	256	—	9 866	8 663	6484	5204	45·5	42·3	24·6	20·5	38·5	33·8
10	208	124	45	45	252	—	9 699	5 814	5821	4391	46·6	46·8	23·4	30·0	38·4	23·0
11	183	160	48	38	165	—	7 376	5 704	4266	3501	40·3	35·7	18·6	17·0	46·5	34·5
12	153	130	70	52	213	—	9 081	6 297	5076	4440	59·4	48·4	33·2	34·2	42·6	29·5
Mean	187	152	54	45	216	—	9 923	7 424	5268	4344	53·7	49·7	25·0	25·2	46·7	34·7
± SD	± 24	± 30	± 9	± 6	± 35	—	± 1 743	± 1 706	± 800	± 577	± 11	± 12	± 4·7	± 6·3	± 8·6	± 8·2
P		< 0·05		< 0·05				< 0·001		< 0·001		NS		NS		< 0·001
Group IIb (myocardial infarction)																
13	166	139	51	40	—	—	9 948	7 551	4825	3850	59·1	54·3	23·1	23·4	—	—
14	265	241	38	21	—	—	11 270	9 388	4645	3204	42·5	38·9	15·4	9·9	—	—
15	154	129	50	48	—	—	10 888	10 169	5185	5109	70·7	78·8	31·5	40·4	—	—
16	266	233	34	32	—	—	8 312	7 489	5136	5623	31·2	32·1	16·9	20·3	—	—
17	308	233	31	27	—	—	7 901	6 084	5219	4136	25·7	27·2	16·9	17·7	—	—
18	207	183	42	30	—	—	5 478	5 126	3885	3168	26·4	28·2	19·3	17·3	—	—
19	197	149	46	38	—	—	7 949	7 356	5077	4415	40·4	49·4	22·6	21·3	—	—
20	182	163	47	41	—	—	7 690	8 608	5246	5343	42·1	53·1	28·8	32·8	—	—
21	230	236	34	34	—	—	7 411	8 857	4067	4733	32·2	37·5	17·7	20·1	—	—
22	280	283	41	29	—	—	6 260	4 972	4277	3300	22·4	17·6	15·3	11·7	—	—
Mean	226	199	41	34			8 311	7 560	4756	4288	39·4	41·7	20·8	21·5	—	—
± SD	± 52	± 53	± 7	± 8			± 1 880	± 1 757	± 513	± 907	± 16	± 18	± 5·7	± 9·2	—	—
P		< 0·05		< 0·001				NS		NS		NS		NS	—	—
Group II (all patients with CAD)																
Mean	211	181	46	38			8 913	7 509	4948	4309	44·5	44·7	22·3	22·9	—	—
± SD	± 47	± 50	± 10	± 9			± 1 942	± 1 681	± 661	± 778	± 15·4	± 15·9	± 5·6	± 8·2	—	—
P		< 0·001		< 0·001				< 0·001		< 0·001		NS		NS	—	—

a, b = atrial pacing 80 and 120/min, respectively.

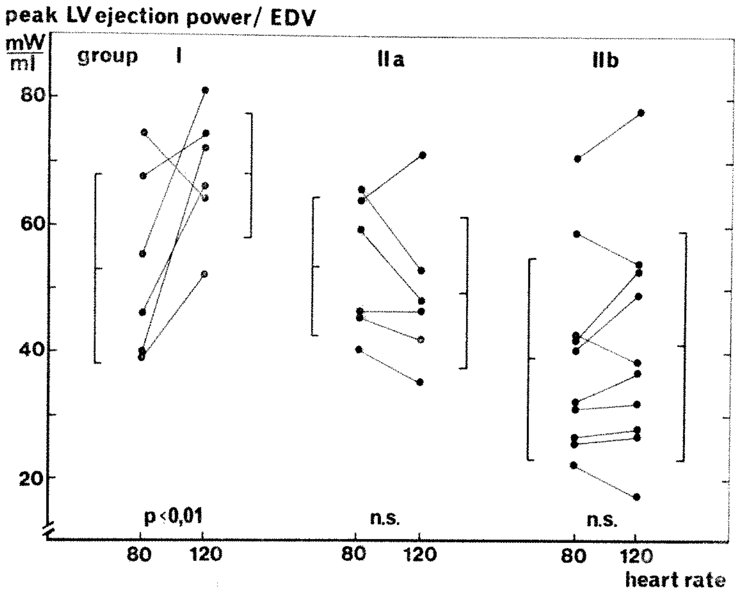

Fig. 2 *Peak left ventricular ejection power normalised by end-diastolic volume. Normals (I) and patients with coronary artery disease without myocardial infarction (IIa) and after myocardial infarction (IIb). Atrial pacing 80 and 120/min.*

At 120/min, however, it rose 28 per cent in group I but remained unchanged in both coronary groups—a significant difference (group II as a whole, $P < 0{\cdot}01$, group IIa, $P < 0{\cdot}02$, and group IIb, $P < 0{\cdot}01$) (Fig. 2). Mean power normalised by end-diastolic volume was significantly higher at 80/min in normal subjects when compared with group IIb ($P < 0{\cdot}02$) and group II as a whole ($P < 0{\cdot}05$) but not with group IIa. At 120/min the difference achieved significance for all coronary groups (IIa, $P < 0{\cdot}05$, IIb, $P < 0{\cdot}02$, and group II as a whole, $P < 0{\cdot}02$), the increase in rate producing a 19 per cent rise in normal subjects but no change in the coronary patients (Fig. 3).

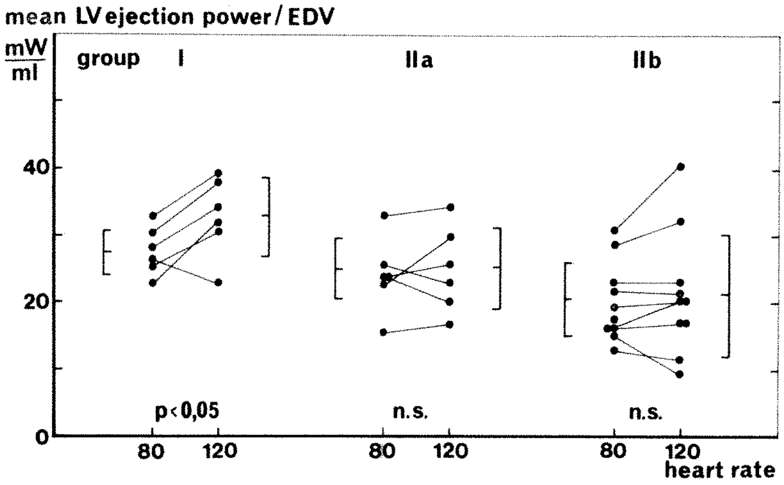

Fig. 3 *Mean left ventricular ejection power normalised by end-diastolic volume. Atrial pacing 80 and 120/min. See legend Fig. 2.*

EJECTION TIME

Ejection time as determined from the aortic pressure tracing at heart rates of 80 and 120/min was 273 ± 25 ms and 232 ± ms respectively in group I, 283 ± 20 ms and 236 ± 12 ms respectively in group IIa, 280 ± 27 ms and 227 ± 28 ms respectively in group IIb, and 281 ± 24 ms and 230 ± 23 ms respectively in group II as a whole. The decrease in ejection time was significant in all groups ($P < 0{\cdot}001$) but there was no statistically significant difference between the groups themselves.

LEFT VENTRICULAR MUSCLE MASS

End-diastolic muscle mass in normal subjects at a heart rate of 80/min was 179 ± 25 g. Muscle mass in group IIa was significantly higher than in normal subjects (216 ± 35, $P < 0{\cdot}05$).

PEAK EJECTION POWER NORMALISED BY MUSCLE MASS

Peak ejection power normalised by muscle mass at a heart rate of 80/min was 44·5 ± 8·3 mW/g in normal subjects and 46·7 ± 8·6 mW/g in patients in group IIa (NS). In normal subjects it remained essentially unchanged when the rate was altered to 120/min. In group IIa it decreased by 26 per cent to 34·7 ± 8·2 mW/g ($P < 0{\cdot}001$) (Fig. 4). The difference between normal subjects and patients in group IIa at a heart rate of 120/min was significant ($P < 0{\cdot}05$).

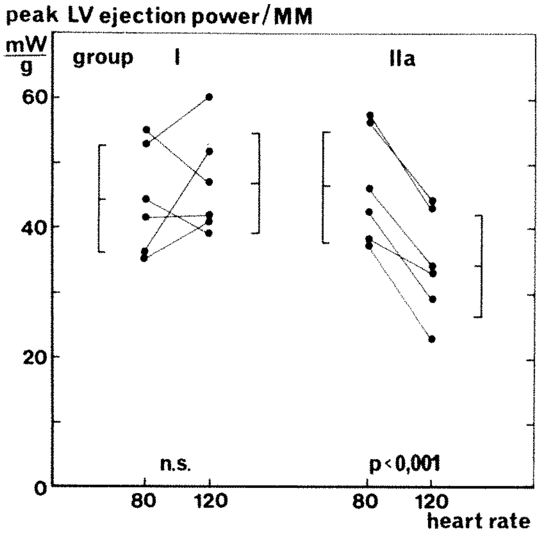

Fig. 4 *Peak left ventricular ejection power normalised by left ventricular muscle mass. Normal subjects (I) and patients with coronary artery disease without myocardial infarction (IIa). Atrial pacing 80 and 120/min.*

Discussion

The left ventricle works as, and is broadly similar to, a mechanical hydraulic pump. In mechanics, pumps are characterised by their peak and mean hydraulic power for a given cycle length and the data needed for the determination of pump power are pressure, volume, and time. However, since ventricular power changes dynamically throughout the cardiac cycle, these indices have to be analysed simultaneously in adequate detail for its study. Furthermore, it is essential to relate ventricular power to a constant cycle length, that is to heart rate.

Bearing these points in mind this investigation was designed to determine the levels of ventricular power during ejection at rest and under stress in normals and in patients with coronary heart disease. Chronic ischaemia of the myocardium as a result of coronary artery stenosis leads to impairment of ventricular pump function, and while this has been shown for other ejection phase indices of ventricular performance (ejection fraction, stroke volume, cardiac output, stroke work, etc. (Sonnenblick and Strobeck, 1977) these do not allow for time, which is an important variable in myocardial dynamics.

Studies of ventricular power in animals and in man have been reported by Chapman *et al.* (1959), Bunnell *et al.* (1962), Hernandez *et al.* (1964), Greenfield *et al.* (1968), and Snell and Luchsinger (1965). Russel *et al.* (1971) and Stein and Sabbah (1976 a, b) investigated left ventricular ejection power in various cardiac abnormalities at rest, but their data can only partly be compared with our own; in particular the heart rate was not kept constant. In our patients, however, this was achieved by the use of atrial pacing, both for basal measurements (at 80/min) and for stress testing (at 120/min). It has been shown previously that rapid atrial pacing is an acceptable method of stressing the heart (Forrester *et al.*, 1971) and in our opinion it is superior to others, such as treadmill testing, pharmacological intervention, or volume loading, for it interferes very little with the systemic circulation in terms of peripheral resistance, mean arterial pressure, and intravascular volume. In addition, it gives results of high reproducibility, which aids the direct comparison of different subjects.

Our findings showed that measured peak left ventricular ejection power under basal conditions was essentially the same in both normal subjects and patients with coronary artery disease, with and without myocardial infarction, though the latter tended to have higher values. This may be explained by the myocardial hypertrophy (increased muscle mass) which was found in this group. However, under stress, peak power fell appreciably in both coronary groups (while in normal subjects it tended to rise) and this fall was statistically significant in the patients without infarction, even though there was no statistical difference in peak left ventricular power at either heart rate *between* the groups. Similar results were obtained for measured mean left ventricular power and it seemed necessary, therefore, to 'normalise' power by relating it to indices which represent the dimension of the ventricle and the mass of its wall. End-diastolic volume, as a measure of muscle fibre length before contraction, was higher in the patients with coronary artery disease than in the normal subjects. This finding is well known (Dwyer, 1970); chronic myocardial ischaemia induces ventricular hypertrophy and dilatation. At the basal heart rate, peak left ventricular power normalised by end-diastolic volume was in the same range in all the 3 groups, though patients with infarction tended to have lower values. When the heart rate was increased, this rose significantly in normal subjects but remained unchanged in both groups of patients with coronary artery disease. Mean left ventricular power normalised by end-diastolic volume, however, was significantly lower at both heart rates in patients with infarction than in normal subjects, and the rate increase led to a rise in this index in normal subjects but not in either coronary group. These results indicate that whereas, normally, ventricular power rises with heart rate, in coronary disease the limited oxygen supply prevents this.

Left ventricular muscle mass was determined in normal subjects and the group without infarction only; it was significantly higher in the latter. Peak power values normalised by muscle mass at rest were in the same range in both, but under stress decreased significantly in the coronary group alone. Similar results were obtained for mean power/g muscle mass. Thus, myocardial hypertrophy in chronic ischaemic heart disease without infarction compensates only in part for loss of pump function. Under moderate stress (here, tachycardia at 120/min) the energy output per unit of muscle mass not only cannot be maintained but indeed falls to critical levels, indicating impending heart failure. This study, then, proves left ventricular power to be of value in delineating myocardial performance at rest and under stress. Further work is needed to determine the influence of the extent and localisation of coronary artery lesions, of arrhythmias, and of drugs, on this measurement.

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Unusual angiographic appearances of the left ventricle in 2 cases of Pompe's disease (glycogenosis type II)

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SUMMARY The angiographic and haemodynamic findings in 2 cases of Pompe's disease (glycogenosis type II) indicated an abnormal trabecular pattern, not previously reported, on the left ventricular angiogram of both patients. This feature may be helpful in distinguishing Pompe's disease from other forms of myocardial abnormality.

Pompe's disease (glycogenosis type II) is an uncommon inherited abnormality of carbohydrate metabolism, characterised by the accumulation of glycogen in skeletal and cardiac muscle. Though several cases have now been reported, and characteristic electrocardiographic findings have been described, there are relatively few reports of the haemodynamic and angiographic features of the disease.

In this report, 2 cases are described with distinctive angiographic features which may be of value in the differentiation from other forms of myocardial disease.

Case reports

CASE 1

The patient was the fourth child in a family with no history of previously affected children. Poor muscle tone was apparent in the neonatal period and the child was seen at the age of 3 months in a neurology clinic because of delay in gross motor milestones. On examination no abnormality was present in the central nervous system, apart from severe hypotonia. The heart sounds were normal and there was no cardiac bruit. Subcostal and intercostal recession was present and shortly after admission the child developed signs of congestive cardiac failure. The chest *x*-ray film showed cardiomegaly (cardiothoracic ratio 0·6) with normal pulmonary vascularity, and the electrocardiographic findings reported in the Table were consistent with those previously reported in this condition (Caddell and Whittemore, 1962; Hohn and Lambert, 1968).

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Echocardiogram

The echocardiogram showed considerable thickening of the interventricular septum (1·4 cm) and posterior left ventricular wall (1·0 cm) compared with the normal values (Meyer, 1977). Motion of the interventricular septum and anterior mitral valve leaflet was normal. The left ventricular end-diastolic and end-systolic dimensions were within the normal range at 2·0 cm and 1·4 cm, respectively, and the percentage change in left ventricular dimension in systole calculated by the method of Gutgesell *et al.* (1977) was 30 per cent. This falls at the

Table *Electrocardiographic and haemodynamic data*

Electrocardiographic data						*Catheterisation data*			
Case	*Rhythm*	*P wave*	*PR(s)*	*QRS*	*T wave*	*RV (mmHg)*	*MPA (mmHg)*	*LV (mmHg)*	*Aorta*
1	Sinus	Normal	0·06	Very high voltages across praecordium; Q wave 14 mm in V6, R wave 66 mm	Biphasic in V5 and V6	30/5	30/10	85/7	—
2	Sinus	Very low voltages in all leads	0·06	Very high voltages across praecordium; Q wave 20 mm in V6, R wave 96 mm	Biphasic in V5 and V6	25/3	25/12	70/10	70/40

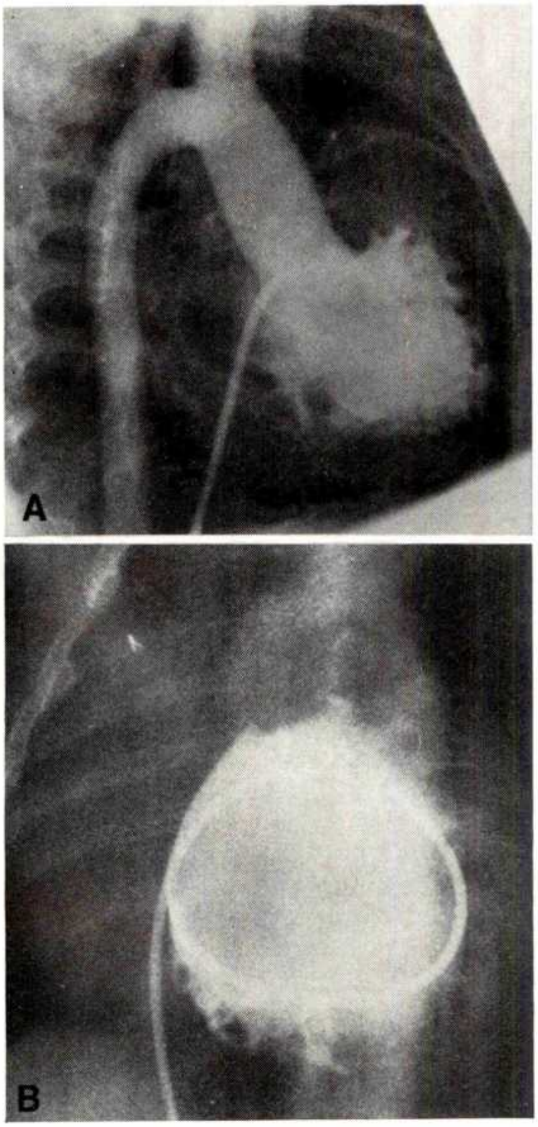

Fig. *Left ventricular angiographic appearances. (A) Left ventricular angiogram in case 1. The unusual trabeculation of the left ventricle is seen. There is no evidence of left ventricular outflow obstruction. (B) Left ventricular angiogram in case 2. The trabeculation at the apex of the left ventricle is unusually prominent, whereas the septal surface is smooth. No evidence of left ventricular outflow obstruction is present.*

lower end of the normal range quoted by these authors.

Cardiac catheterisation and angiography

The investigation was carried out at the age of 4 months with local anaesthesia. No evidence of left-to-right shunting was present but the foramen ovale was patent. A continuous withdrawal tracing across the right ventricular outflow tract showed no pressure gradient, and the left ventricular pressure was not raised. Cineangiograms were obtained from the left and right ventricles. The left ventricular wall was considerably thickened and an abnormally prominent trabecular pattern was present (Fig. A). There was no evidence of left ventricular outflow tract obstruction and the coronary arteries were normal. The right ventricle showed a similar abnormal trabecular pattern. Though the end-diastolic volume of the left ventricle was high, in this patient left ventricular function assessed angiographically was only moderately impaired.

The diagnosis of type II glycogenosis was confirmed by assay of leucocyte α1-4 glucosidase (acid maltase).

CASE 2

The patient is the second child of healthy parents with no history of previously affected children. At the age of 4 months the child was admitted to hospital because of poor feeding and respiratory problems. Physical examination showed obvious hypotonia but no other abnormality in the central nervous system. A grade 2/6 systolic murmur was present at the left sternal border and a third sound was heard at the apex. Evidence of congestive heart failure was present. The chest *x*-ray film showed considerable cardiomegaly (cardiothoracic ratio 0·7) and the electrocardiographic findings are shown in the Table.

Cardiac catheterisation and angiography

The investigation was performed at the age of 4 months under local anaesthesia. No evidence of left-to-right shunting was found but the foramen ovale was patent. Continuous pressure recording during withdrawal showed no gradients across either the left or right ventricular outflow tracts. Cineangiography from the left ventricle (Fig. B) showed the ventricle to be dilated and poorly functioning. The abnormal trabecular pattern seen in case 1 was again apparent, and the ventricular wall was considerably thickened. No evidence of subaortic stenosis was seen and the coronary arteries were normal.

The diagnosis of type II glycogenosis was confirmed by assay of leucocyte α1-4 glucosidase.

Discussion

Relatively few patients with type II glycogenosis have been investigated by cardiac catheterisation and angiography and, among those studied, varying patterns of abnormality have been recorded. Obstruction to left or right ventricular outflow caused by hypertrophy of the interventricular septum has been reported in several cases (Hohn *et al.*, 1965; Rees *et al.*, 1976) but is not universally present. When present, left ventricular outflow obstruction may be severe and surgical treatment has been attempted in 1 case (Ehlers *et al.*, 1962).

The angiographic features of the condition have been described in 6 patients. Ruttenberg and colleagues (1964) described the findings in 2 patients studied by venous angiography, and contrasted the poor left ventricular contractility seen in 1 patient with the relatively good ventricular function seen in the second patient. At necropsy the first patient proved to have associated endocardial fibroelastosis. Hohn *et al.* (1965), Hernandez *et al.* (1966), and Rees *et al.* (1976) each studied single cases in which left ventricular contractility was good. The sixth case, reported by Nihill *et al.* (1970), had a poorly functioning left ventricle, assessed by follow up after a right ventricular angiogram.

Our 2 cases are of particular interest, since an abnormally prominent trabecular pattern was present on the left ventricular angiogram of both patients. Prominent trabeculation has not previously been reported as a feature of the left ventricular angiogram in this condition, but was noted on the right ventricular angiogram of the case described by Hernandez *et al.* (1966) and appears to be present to a lesser extent in the left ventricular angiogram illustrated in the report of Nihill *et al.* (1970). Pathological studies have shown a high incidence of endocardial fibroelastosis in cases of Pompe's disease (Dincsoy *et al.*, 1965). Review of the published cases suggests that those cases with a dilated non-compliant left ventricle are likely to have associated endocardial fibroelastosis, whereas when the ventricle is contracting effectively outflow tract obstruction is more frequent.

During the investigation of infants with pronounced hypotonia and evidence of cardiac abnormality, the presence of distinct trabeculation in the left ventricle should alert the investigator to the possibility of glycogen storage disease of the heart.

The authors thank Dr L. Rosenbloom and Dr J. Owen for permission to study patients under their care; Dr R. Galloway for permission to reproduce the angiograms; and the Department of Biochemistry, Charing Cross Hospital, for performing the enzyme assay.

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Double outlet right ventricle with subvalvular aortic stenosis[1]

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SUMMARY A case of double outlet right ventricle had progressive muscular subvalvular aortic stenosis unrelated to the ventricular septal defect. Ventricular systolic pressures were identical and higher than aortic, and the gradient was within the right ventricle. Selective angiocardiography showed a hypertrophied subaortic conus obstructing the right ventricular outlet. Serial haemodynamic and angiographic studies revealed progression of the subaortic stenosis which may have been related to an earlier pulmonary artery banding operation. Distal conal hypertrophy is postulated as the cause of the obstruction.

The anatomical, pathophysiological, medical, and surgical aspects of double outlet right ventricle are well known. Edwards *et al.* (1952), Lauer *et al.* (1960), Neufeld *et al.* (1961a, b), Cheng (1962), Serratto *et al.* (1967), Mason *et al.* (1969), Lavoie *et al.* (1971), Rao and Sissman (1971), Megarity *et al.* (1972), Pellegrino *et al.* (1973), Goor and Lillehei (1975), and Cameron *et al.* (1976) have described complex variants of this lesion including associated mitral stenosis or atresia, pulmonary stenosis or atresia, coarctation of the aorta, persistent ductus arteriosus, and left ventricular obstruction from a restrictive ventricular septal defect. Left ventricular obstruction caused by subvalvular aortic stenosis has been cited by Mason *et al.* (1969) and by Spidaromont *et al.* (1976). We present haemodynamic and angiographic evidence of a patient with double outlet right ventricle with progressive muscular subaortic stenosis.

Case report

This 14-month-old girl weighed 2410 g at birth after a 37-week uncomplicated gestation. Within 2 hours of age she was found to have jejunal atresia. Shortly thereafter she developed congestive heart failure. Digoxin and frusemide improved her cardiac status and she successfully underwent abdominal surgery at 2 days of age. Cardiovascular examination disclosed a tachypnoeic, acyanotic infant whose lungs were clear to auscultation. The arterial pulses were normal. The praecordium was hyperactive and the point of maximum impulse was diffuse along the left sternal border. The second heart sound was split and there was a loud third sound at the apex. A grade 3/6 long systolic ejection murmur was heard along the left sternal border. A mid-diastolic rumble was present at the apex. The liver was palpable 3 cm below the right costal margin. The electrocardiogram and vectorcardiogram showed right ventricular hypertrophy and the chest *x*-ray film showed cardiomegaly, with increased vascularity.

At 2 weeks of age, cardiac catheterisation showed a torrential pulmonary blood flow, and equal systolic pulmonary artery, aortic, and ventricular pressures (Table). Cineangiography showed a double outlet right ventricle with a large ventricular septal defect and suggested muscular subaortic stenosis (Figs 1 and 2). At 3 weeks of age, she underwent pulmonary artery banding and went home at 5 weeks of age much improved.

At 14 months, she presented as a small, comfortable, acyanotic toddler. The praecordium was slightly hyperactive and there was a thrill at the upper left and right sternal borders. The first heart sound was normal. The second heart sound was well split. There was a long harsh systolic ejection murmur maximal at the mid left sternal border radiating to the upper right and left sternal borders. A short mid-diastolic rumble was present at the apex. A sharp liver edge was palpable 2 cm

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Table *Cardiac catheterisation data*

Site	*Pressure (mmHg)*		*O_2 sat. (%)*		*Pressure (mmHg)*		*O_2 sat. (%)*
Superior vena cava			58				62
Right atrium		$\overline{m} = 2$	71‡			$\overline{m} = 5$	56
Right ventricle	77/4		89		164/12		
Main pulmonary artery	78/25	$\overline{m} = 51$	87	*Prox.	123/12	$\overline{m} = 66$	
				†Dist.	24/10	$\overline{m} = 14$	82
Left atrium		$\overline{m} = 8$				$\overline{m} = 9.5$	
Aorta	72/30	$\overline{m} = 51$	89		80/45	$\overline{m} = 63$	93
Left ventricle	70/7		89		164/14		93
Pulmonary blood flow (l/min per m^2)	8·9				8·7		
Systemic blood flow (l/min per m^2)	2·0				4·1		
Pulmonary to systemic blood flow	4·5 : 1				2·4 : 1		
Pulmonary vascular resistance (mmHg/l per min per m^2)	4·8				0·6		
Systemic vascular resistance (mmHg/l per min per m^2)	24·5				15·9		

*Proximal to band.
†Distal to band.
‡Left-to-right shunt at the atrial level, probably through a 'stretched' patent foramen ovale.

below the right costal margin. The electrocardiogram and vectorcardiogram showed combined ventricular hypertrophy. There was cardiomegaly and increased pulmonary vascularity on chest *x*-ray film. At repeat study there was moderately increased pulmonary blood flow (pulmonary: systemic flow ratio = 2·4), and manometry showed equal systolic ventricular pressures exceeding aortic pressure, and proximal main pulmonary arterial pressure exceeding aortic and distal pulmonary arterial pressures. In addition, there was a 41 mmHg subpulmonary gradient. Cineangiography showed a double outlet right ventricle, adequate pulmonary artery band, subvalvular pulmonary stenosis and severe subaortic stenosis, and a large ventricular septal defect (Table; Fig. 3).

Discussion

Cases of double outlet right ventricle with left

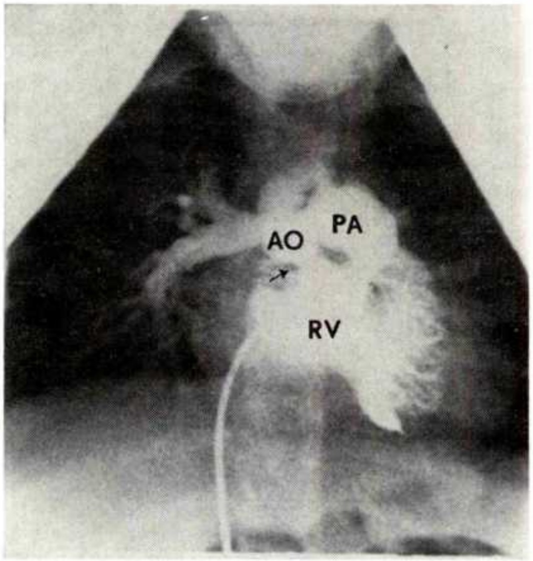

Fig. 1 *Selective right ventricular angiogram in the anteroposterior view shows the right ventricular origin of the aorta from a narrowed subaortic conus (arrow) to the right of the pulmonary artery. Abbreviations: AO, aorta, PA, pulmonary artery, RV, right ventricle.*

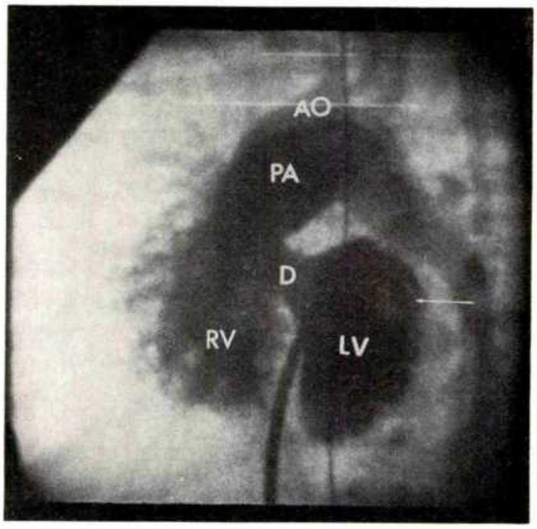

Fig. 2 *Left ventricular cineangiocardiogram in left anterior oblique projection, showing the large ventricular septal defect (D), associated with double outlet right ventricle. The arrow shows the mitral valve, indicating the absence of aortic-mitral valve continuity. Abbreviations: AO, aorta, PA, pulmonary artery, RV, right ventricle, LV, left ventricle.*

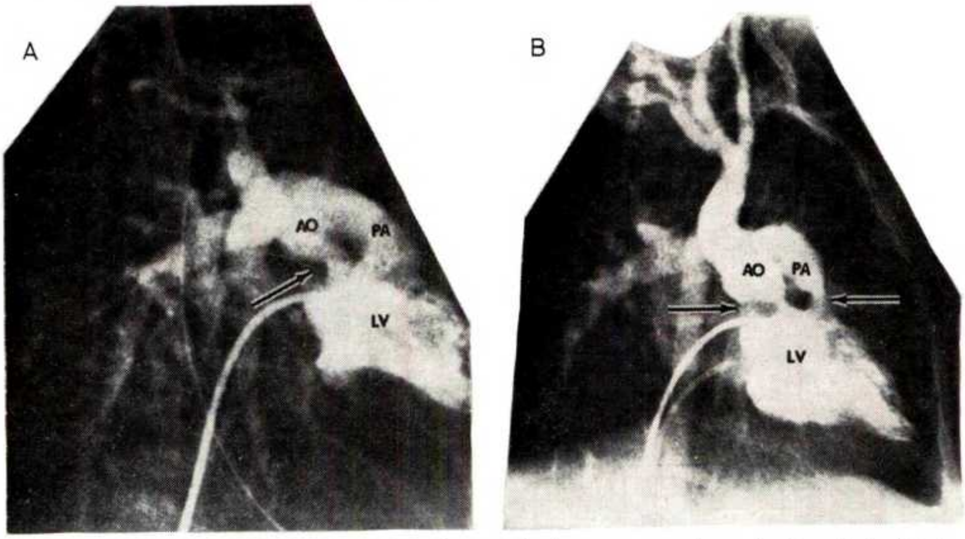

Fig. 3 *Selective left ventricular cineangiocardiograms in the anteroposterior projection obtained during the first (A) and second (B) cardiac catheterisations, showing the progression of the muscular subaortic stenosis (left-sided arrows). The right-sided arrow in (B) shows the moderately severe subpulmonary stenosis. Abbreviations: AO, aorta, LV, left ventricle, PA, pulmonary artery.*

ventricular obstruction from a restrictive ventricular septal defect, reported by Edwards *et al.* (1952), Lauer *et al.* (1960), Neufeld *et al.* (1961a, b), Cheng (1962), Serratto *et al.* (1967), Mason *et al.* (1969), Lavoie *et al.* (1971), Rao and Sissman (1971), Megarity *et al.* (1972), and Pellegrino *et al.* (1973), have shown the systolic pressure of the left ventricle to be higher than that of the right ventricle, and equal systolic pressures in the right ventricle and in the aorta.

In 2 of 88 cases reported by Spidaromont *et al.* (1976) subaortic stenosis was suggested by a systolic pressure gradient between the right ventricle and aorta. There were no left ventricular pressures or angiographic data available in their cases. They suggested that the obstruction was the result of a hypertrophied parietal band. Mason *et al.* (1969) described angiographic and intraoperative findings of a double outlet right ventricle with aortic obstruction from a subaortic membrane. However, there was no gradient between the aorta and right ventricle.

The present case of double outlet right ventricle is unique as equal ventricular systolic pressures, a progressive subaortic systolic gradient, and angiographic findings of progressive muscular subaortic obstruction are shown. At 2 weeks of age there was no gradient between right ventricle and aorta, though angiographically there was evidence of obstruction. The absence of a gradient may have been related to the diminished systemic flow index.

At 14 months, she had grown and the systemic flow index increased. A gradient of 78 mm was then found between the inflow and the subaortic regions of the right ventricle and the subaortic obstruction was more severe angiographically.

According to Griepp *et al.* (1974), subpulmonary stenosis is known to occur after a pulmonary artery band caused by hypertrophy of the subpulmonary distal conal septum. In double outlet right ventricle the distal conal septum lies beneath both great arteries. We suggest that hypertrophy of the subpulmonary component may have displaced the subaortic portion to the right, and that displacement and hypertrophy of the subaortic conus has led to subaortic obstruction in our case.

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Effects of propranolol in a case of orthostatic hypotension

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SUMMARY In a hypertensive patient with orthostatic hypotension, the changes in several haemodynamic indices with respect to posture were evaluated. In the upright position, systemic blood pressure was reduced as compared with the supine position, and peripheral vasodilatation was present, as shown by an increase in Jantsch's index of the impedance plethysmographic tracings. Systolic time intervals remained unchanged with changes in posture. Propranolol 10 mg intravenously brought the response to normal. In fact, after beta-blockade in the standing position the blood pressure remained unchanged and normal peripheral vasoconstriction was observed. Similar results were seen during atrial pacing at a constant heart rate of 130 beats/minute. In this patient, propranolol appears to normalise the response to the posture change, by restoring normal vasoconstriction in the upright position.

Orthostatic hypotension has been classically defined as a reduction in arterial pressure on standing. This uncommon disorder is probably related to sympathetic nervous dysfunction induced either by certain diseases, such as diabetes mellitus (Sharpey-Schafer and Taylor, 1960), hypertension (Drenick, 1957; Lewis and Dunn, 1967; Božović *et al.*, 1970) and other disorders (Ibrahim *et al.*, 1975), or by different drug treatments (Parra and Vidrio, 1969; Ibrahim *et al.*, 1975). An idiopathic form of orthostatic hypotension, sometimes associated with tachycardia, is also known (MacLean *et al.*, 1944; Scherba, 1954). Propranolol has been suggested (Miller *et al.*, 1974) in the treatment of orthostatic hypotension on the assumption that beta-blockade, by reducing orthostatic tachycardia, would increase cardiac output and stabilise arterial pressure.

The present study was designed to assess the effects of propranolol administration in a hypertensive patient affected by orthostatic hypotension, with no pronounced tachycardia.

Case report and methods

A 62-year-old man was admitted to hospital because of hypertension and increasing weakness and lightheadedness on standing. Supine arterial pressure ranged between 170/110 and 180/120 mmHg; on standing, the arterial pressure decreased to levels as low as 130/100 mmHg. Heart rate showed only a minimal increase in the upright position. A detailed evaluation, including thyroid and adrenal gland functions, disclosed no abnormality. Plasma renin values were 198 ng/100 ml. No significant amounts of catecholamines or their metabolites were found in urine samples. The patient did not take hypotensives or any other drug before or during his stay in hospital.

According to Ibrahim (1975), a preliminary study was performed to verify the integrity of each of the individual components of the baroceptor reflex arch. This was done by testing changes in systemic blood pressure during hyperventilation, mental arithmetic, and cold pressor tests.

Thereafter, in the supine position, electrical impedance plethysmography was carried out on both legs of the subject, to derive a noninvasive index of blood flow. This plethysmographic method, described elsewhere (Nyboer, 1970; Nyboer *et al.*, 1974), was chosen because, by surface impedance electrodes the segmental volemic conditions can be best defined without abnormal segmental compression, or crude air or water-tight encasement, always required for mechanical plethysmography. Electrocardiogram, phonocardiogram, and carotid pulse were recorded on an Electronics for Medicine photographic recorder; this was done in order to obtain systolic time intervals (STI), which correlate well with invasive indices of cardiac performance (Weissler *et al.*, 1961; Metzer *et al.*, 1970). Arterial pressure was measured simultaneously by a cuffed manometer and heart rate was derived from the electrocardiogram. All these recordings were then repeated with the patient in the standing position.

Subsequently, propranolol (10 mg) was administered intravenously and the entire procedure was repeated both in the supine and upright position.

Finally, 3 hours after the administration of the drug, when heart rate and arterial pressure had returned to previous values, a temporary transvenous cardiac pacemaker was implanted and the procedure was repeated at a constant heart rate of 130 beats/min before and after a new dose of propranolol 10 mg intravenously. Left ventricular ejection time (LVET), LVET corrected for heart rate (LVETc) (Weissler *et al.*, 1969), pre-ejection period (PEP), and isometric contraction time (ICT) were calculated according to the methods of Py and Meurin (1971); in order to quantify the changes in the plethysmographic waves, the Jantsch index was calculated for each tracing (Jantsch, 1958). In order to assess the reproducibility of the results, the study was repeated after 48 hours.

Written consent was obtained from the patient before the study.

Results

The preliminary tests indicated that the lesion was at the periphery of the baroceptor reflex arch, since abnormal responses were measured during all of the tests (Table).

Table *Effect of tests of autonomic function on arterial pressure in a patient with orthostatic hypotension*

	Blood pressure (mmHg)		
	Systolic	*Diastolic*	*Mean*
Supine	175	115	135
Tilt up	130	100	110
Cold pressor test	165	110	128·3
Mental arithmetic	160	100	120
Hyperventilation	165	100	121·5

SINUS RHYTHM

Before propranolol

Arterial pressure, which was 175/115 mmHg in the supine position, decreased to 130/100 mmHg when upright, while heart rate rose from 95 to 98 beats/min (Fig. 1). The LVETc decreased from 392 to 386 ms on standing. PEP and ICT remained unmodified (100 and 20 ms, respectively). The postural change induced an increase in Jantsch's index in both legs, from 0·70 to 0·94 in the right and from 0·76 to 0·95 in the left limb (Fig. 1).

After propranolol

Arterial pressure showed minimal change from supine (170/110 mmHg) to standing position (175/110 mmHg) and heart rate increased from 82 to 92 beats/min (Fig. 1). LVETc was prolonged from 371 to 377 ms. No change was seen in PEP and ICT (110 and 30 ms, respectively). The Jantsch index decreased in both legs, from 0·66 to 0·55 and from 0·70 to 0·60 in the right and left leg, respectively (Fig. 1).

DURING ATRIAL PACING

Before propranolol

Arterial pressure decreased from 180/120 to 130/100 mmHg on standing (Fig. 2); LVETc decreased from 408 to 393 ms and PEP and ICT were unchanged (130 and 30 ms, respectively). The Jantsch index rose in both legs in the erect position from 0·63 to 0·75 in the right leg and 0·70 to 0·87 in the left leg (Fig. 2).

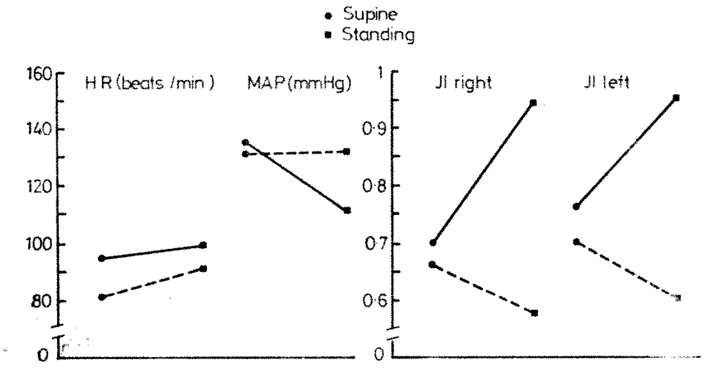

Fig. 1 *Effects of standing on heart rate (HR), mean arterial pressure (MAP), and Jantsch index (JI) in the left and right leg, before (solid line) and after (dotted line) propranolol (10 mg i.v.).*

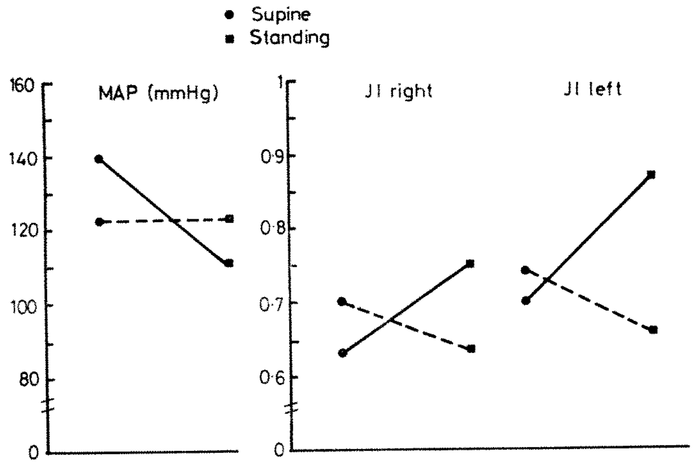

Fig. 2 *Effects of standing on mean arterial pressure (MAP) and the Jantsch index (JI) in the left and right leg, before (solid line) and after (dotted line) propranolol (10 mg i.v.) during atrial pacing at 130 beats/min.*

After propranolol
Arterial pressure was 150/110 mmHg in the supine position and on standing (Fig. 2). LVETc was prolonged from 408 to 418 ms while PEP was 130 ms in the supine and upright position and ICT was 30 ms in both positions. The Jantsch index decreased from 0·70 to 0·63 in the right leg and 0·74 to 0·66 in the left (Fig. 2). The entire procedure was repeated after 48 hours and very similar results were obtained.

Discussion

Propranolol has recently been suggested for treating orthostatic hypotension since its effects on heart rate could normalise cardiac output impaired by orthostatic tachycardia (Miller *et al.*, 1974).

The patient studied in this report showed distinct hypotension on standing. This was accompanied by a modest increase in heart rate. Moreover, in the upright position there was an increase in flow in the peripheral vascular bed, as reflected by a rise in the Jantsch index.

The change in posture was not accompanied by any discernible change in stroke volume, as shown by the minimal change in LVETc. This observation rules out the possibility that the observed hypotension is dependent on a decrease in cardiac output. It indicates that the increase in the Jantsch index could be related only to peripheral vasodilatation, which takes the place of the normal postural vasoconstriction.

During atrial pacing at 130 beats per minute similar results were obtained, thus showing that an increase in heart rate will not modify this response.

Propranolol administration can inhibit the decrease in arterial pressure on standing. This event is accompanied by a small increase in LVETc and normal postural vasoconstriction as shown by the decrease in the Jantsch index. Similar results were observed during atrial pacing, thus showing that the stabilising effects of beta-blockade on arterial pressure are not related to reduced heart rate. Propranolol administration modified the vasodilatation induced by posture change, restoring the normal vasoconstrictive response. As a consequence, the abnormal reflex response in the peripheral vascular bed seems to be the haemodynamic factor responsible for the reduction in arterial pressure with upright posture. This conclusion is in agreement with a previously reported hypothesis (Ibrahim *et al.*, 1974), as well as recent studies suggesting that lesions in the efferent sympathetic pathways are the predominant findings in orthostatic hypotension (Ibrahim *et al.*, 1975). On the other hand, other studies have shown the participation of both alpha- and beta-receptors in the regulation of posture related arterial reflexes (Rengo *et al.*, 1976). Accordingly, the orthostatic hypotension in this patient could be the result of a disturbance of balance in the peripheral sympathetic nervous system, caused by peripheral beta-receptor hypersensitivity, or by alpha-receptor fatigue (Luria *et al.*, 1964).

In conclusion, the beta-receptor blockade induced in this patient seems to allow the action of catecholamines mainly on the alpha receptors, thus restoring the normal postural vasoconstriction.

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Requests for reprints to Dr Gregorio Brevetti, Istituto di Patologia Speciale Medica, II Facolta di Medicina e Chirugia, Via Sergio Pansini 5, 80131 Napoli, Italy.

British Heart Journal, 1979, **41**, 249-252

Corrected transposition of great vessels and Ebstein's anomaly of tricuspid valve

Echocardiographic findings

JAMES G. HENRY, SEYMOUR GORDON, AND GERALD C. TIMMIS

From the Division of Cardiovascular Diseases, William Beaumont Hospital, Royal Oak, Michigan, USA

SUMMARY A case is reported concerning echocardiographic findings in a patient with congenital corrected transposition of the great vessels and Ebstein's anomaly of the tricuspid valve. This presented an unusual opportunity to study atrioventricular valve closure in a patient in whom the Ebstein's malformation involved the systemic atrioventricular valve. The mitral to tricuspid valve closure interval was 68 milliseconds and represented significant delay in tricuspid valve closure. This closure interval is similar to closure intervals previously reported for patients with Ebstein's anomaly without ventricular inversion.

Recent echocardiographic studies have detailed the timing of atrioventricular valve closure in Ebstein's anomaly of the tricuspid valve (Kotler and Tabatznik, 1971; Lundström, 1973; Farooki *et al.*, 1976; Milner *et al.*, 1976). These studies indicate the diagnostic value of delayed tricuspid closure. The mechanism of delayed tricuspid closure is speculative (Lundström, 1973; Milner *et al.*, 1976). The patient described here provided an opportunity to study atrioventricular valve closure in ventricular inversion (congenital corrected transposition of the great vessels) and Ebstein's malformation of the systemic atrioventricular valve.

Case report

A 22-month-old girl was admitted for further cardiovascular diagnostic studies. A diagnosis of corrected transposition of the great vessels and regurgitation of the systemic atrioventricular valve had been made by cardiac catheterisation and angiocardiography at 3 weeks of age. In the ensuing 21 months, she showed slow growth and frequent respiratory infections. Re-evaluation at 22 months revealed a small, thin, acyanotic toddler in no distress. There was a hyperdynamic impulse in the left parasternal area. A pansystolic murmur was present at the lower left sternal border and apex. An apical mid-diastolic murmur was present. The second heart sound was single and accentuated. The liver was palpable 2 cm below the right costal margin.

An electrocardiogram revealed a QRS duration of 0·10 s (lead II). Slurring of the upstroke of the R wave was present in leads I, V5, and V6.

Cardiac catheterisation (Table) disclosed moderate pulmonary arterial hypertension, raised pulmonary arterial wedge pressures, and a marginally significant increase in oxygen saturation between systemic venous and pulmonary arterial blood. Cineangiocardiography with selective opacification of systemic and pulmonary ventricles showed ventricular inversion and 1-transposition of the great vessels. Displacement of the tricuspid valve leaflets distally into the sinus of the right ventricle was noted (Fig. 1), producing an angiographic picture previously described in Ebstein's malformation of the tricuspid valve with ventricular inversion (Jaffee,

Table *Catheterisation data*

Site	*% Oxygen saturation*	*Pressure (mmHg) systolic/diastolic*
Superior vena cava	64	
Inferior vena cava	71	
Right atrium	72	a = 6, v = 5, mean = 3
Left ventricle	72	49/5
Pulmonary artery	72	51/24 mean = 36
Pulmonary capillary	98	a = 24, v = 24, mean = 18
Right ventricle	96	78/6
Aorta	96	79/53 mean = 67

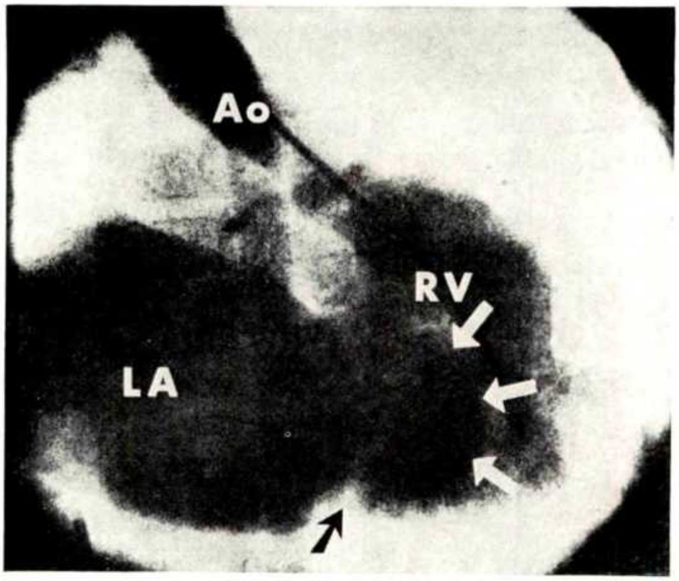

Fig. 1 *Anteroposterior projection of systemic ventricular cineangiocardiogram. The ventricle is coarsely trabeculated and has an infundibulum separating the systemic atrioventricular valve from the aortic valve. The black arrow indicates the atrioventricular valve ring. The 3 white arrows indicate the displaced tricuspid valve leaflet. Note distinct tricuspid regurgitation into the enlarged left atrium. Ao, aorta; LA, left atrium; RV, anatomical right ventricle.*

1976). Pronounced tricuspid regurgitation was observed.

ECHOCARDIOGRAPHIC TECHNIQUE AND RESULTS

Echocardiographic recordings were performed with an Ekoline 20 ultrasonoscope and a 3·5 mHz 1/4 in transducer. A Cambridge strip chart recorder was used with 100 mm per second paper speed and 40 millisecond time lines.

The patient was examined in the supine position. The atrioventricular valves were identified by their relation to semilunar valves as described by Solinger *et al.* (1974). The posterior, left atrioventricular valve (tricuspid) was easily recorded in the 3rd and 4th intercostal spaces in a wide area from the left sternal border to the left midclavicular line. The anterior, right atrioventricular valve (mitral) was recorded only with medial angulation at the lower left sternal border.

Atrioventricular valve closure was identified by the point of coaptation of leaflets, or in the case of the tricuspid valve, that instant at which the two recorded leaflets sharply terminated their rapid approximation at the onset of systole (Mc and Tc in Figs 2 and 3).

The interval between echocardiographic closure of the mitral and tricuspid valves (McTcI) was determined as follows:

The interval between the Q wave of the electrocardiogram and mitral closure (Q-Mc) was determined by measurement of the interval to the nearest 5 milliseconds in 5 successive complexes with nearly identical RR intervals and taking the average value. The interval between the Q wave of the electrocardiogram and tricuspid closure (QTc) was determined in the same manner. McTcI was obtained by subtracting mean QMc from mean QTc. Heart rates during recordings for determination of QMc and QTc were similar, averaging 111 and 114 per minute, respectively.

The value obtained for McTcI was 68 milliseconds.

Discussion

The patient reported here has ventricular and atrioventricular valvular inversion. Thus the posterior, systemic atrioventricular valve is tricuspid. In addition, this posterior atrioventricular valve had the angiographic appearance of Ebstein's anomaly (Jaffee, 1976).

This case report is of value in two respects:

(1) It represents one of the few reported instances of echocardiographic closure of the anterior atrioventricular valve before closure of the posterior atrioventricular valve. To our knowledge this sequence of atrioventricular valve closure has been reported in only one normal subject (Milner *et al.*, 1976) and has been reported as the usual finding in only one congenital cardiac defect, classical complete transposition of the great vessels (Milner *et al.*, 1976).

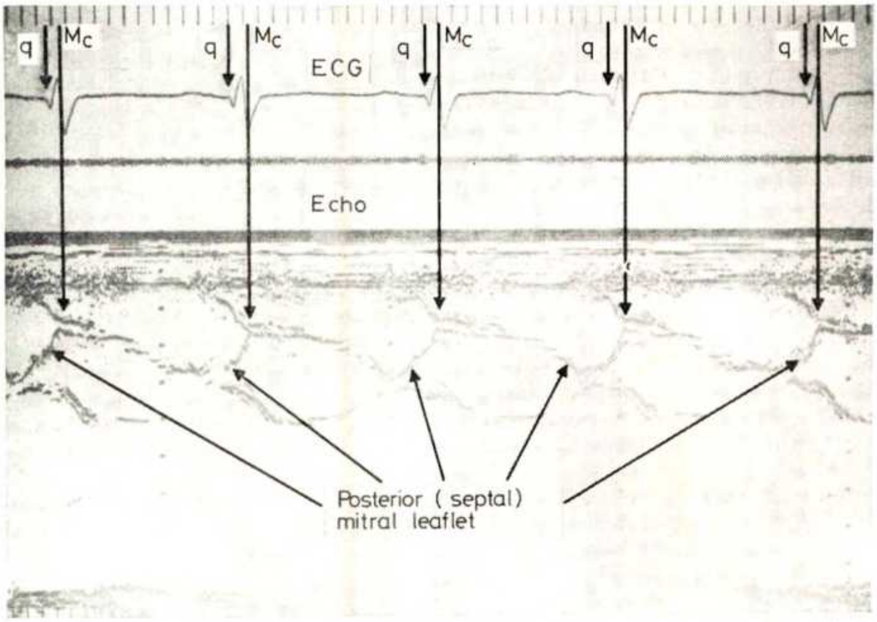

Fig. 2. *Mitral valve echoes in corrected transposition of the great vessels. Echo, echocardiogram, ECG electrocardiogram; Mc, mitral closure point; q, initiation of Q wave of the electrocardiogram.*

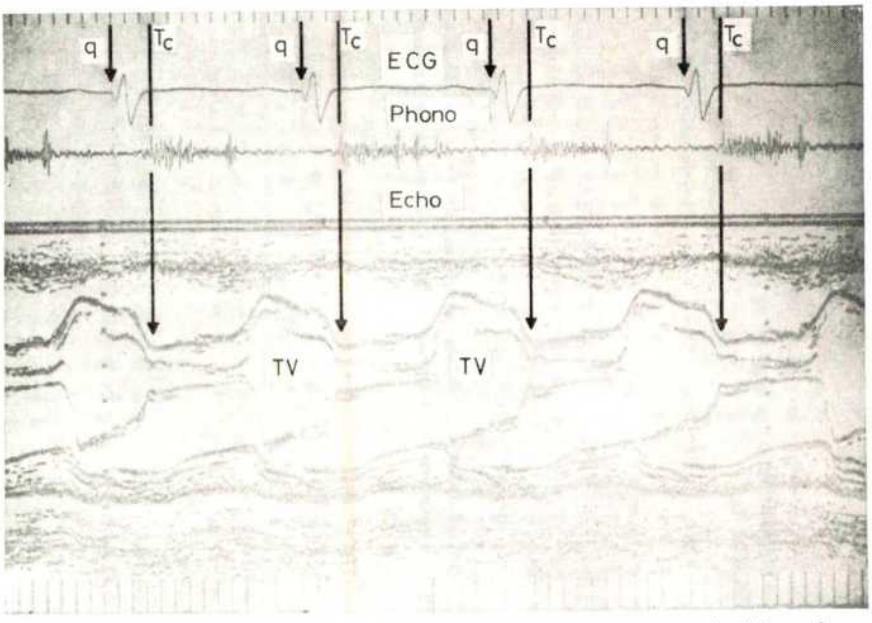

Fig. 3 *Tricuspid valve echoes in corrected transposition of the great vessels. Echo, echocardiogram; ECG, electrocardiogram; Phono, phonocardiogram; q, initiation of Q wave of the electrocardiogram; Tc, tricuspid closure point; TV, tricuspid valve echoes.*

(2) Delayed tricuspid valve closure was demonstrated echocardiographically in this patient with ventricular (and therefore atrioventricular valvular) inversion and Ebstein's anomaly of the tricuspid valve. The delay in tricuspid valve closure expressed as the McTc interval was 68 milliseconds and is in the range reported for Ebstein's anomaly without ventricular inversion (Kotler and Tabatznik, 1971; Lundström, 1973; Farooki *et al.*, 1976; Milner *et al.*, 1976). Thus delayed tricuspid valve closure is apparently a feature of Ebstein's malformation of the tricuspid valve in ventricular inversion as well as in ventricular noninversion.

Further echocardiographic studies in patients with and without Ebstein's malformation, ventricular inversion, and great vessel malformations will be required to test the diagnostic value of the observations cited in this case report.

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Am. Heart J. (1976) **92,** 455, Battock DJ et al. Effects of isosorbide dinitrate and nitroglycerin on central circulatory dynamics in coronary artery disease.

Am. J. Cardiol. (1977) **39,** 91, Bussmann WF et al. Orally administered isosorbide dinitrate in patients with and without left ventricular failure due to acute myocardial infarction.

Circulation (1977) **55,** 381, Danahy DT et al. Sustained hemodynamics and antianginal effect of high dose oral isosorbide dinitrate.

Am. J. Cardiol. (1977) **39,** 84, Williams DO et al. Hemodynamic assessment of oral peripheral vasodilator therapy in congestive heart failure: prolonged effect of isosorbide dinitrate.

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British Heart Journal, 1979, **41**, 253-254

Systolic time intervals and impedance cardiography

Sir,

The pair of papers from the New Delhi group (Balasubramanian *et al.* (1978), *British Heart Journal*, **40**, 268, 276) are worthwhile contributions to the practical use of systolic time intervals based on impedance cardiography as well as providing interesting data on the effects of altitude. I take exception, however, to an important methodological aspect—correction of the pre-ejection period (PEP) for heart rate. Not only does pure rate change (atrial pacing) fail to change the PEP, but also a burgeoning literature (partially cited in Spodick, 1977) shows that any seeming pre-ejection period-heart rate (PEP-HR) relation is at best at very low level (r usually $\leqslant 0{\cdot}2$ and nonsignificant) and, in any case, probably associated with a common factor (for example adrenergic stimulation) which affects both HR and PEP *pari passu*; that is, no direct relation. Indeed, the latest evidence of this appeared in the immediately preceding paper in the same number of the *British Heart Journal* (Wikstrand *et al.*, 1978). This is of more than theoretical interest, particularly when one inspects Table 1 of the authors' paper on altitude effects. There, if the PEP is recalculated from the 'rate-corrected' PEP (by subtracting 0·44 HR from the latter), there is almost no difference between the mean values and control PEP on all days excepting for small increases on days 5 and 10. The PEPs in ms from day one, 0 to 4 h, to day 10 are as follows: 95, 96, 95, 96, 96, 102, 100. After return to sea level the PEP was: 93, 94, 92. Similarly, in Table 2, the difference between sea-level PEP and day 10 at altitude is reduced from 17 ms ('rate-corrected') to only 6 ms (possibly significant but probably at a much lower level). Clearly, if, as so many contend, HR is not really related to PEP, there was little if any change in PEP. (On the other hand, if, as the authors imply, HR is related to PEP the changes in HR alone would account for most or all the altitude changes in PEP.)

I must also point out a misleadingly infelicitous turn of phrase in citing some of our work (Spodick and Lance, 1976). The authors state that we 'discussed the possibility' of eliminating the need for a phonocardiogram for recordings made during exercise performance. This is quite inaccurate. Far from discussing a 'possibility', we showed quite clearly that it can be done. Indeed, had the authors adopted this method, they might have solved some of their technical problems, including the problem of getting measurements during actual exercise performance. The argument that we used a peripheral pulse does not (as we demonstrated) affect the validity of the systolic time interval responses. Moreover, recent work has shown (Nandi and Spodick, 1977) that within the first 15 seconds after the conclusion of bicycle exercise the LVET continues to fall and then begins to rise. Thus, small differences among subjects in the exact timing of a post-exercise recording could produce widely divergent individual responses, impairing the validity of any group mean.

The foregoing considerations leave the body of information in these papers intact and show the utility of the impedance cardiogram. The authors and other workers may be interested in the proceedings of the Association for the Advancement of Medical Instrumentation (AAMI, Washington, D.C., March 1978). The session on impedance cardiography documented major advances in theory, technique, and applications.

David H. Spodick,
University of Massachusetts
Medical School,
Division of Cardiology,
St Vincent Hospital,
Worcester, Mass. 01604, USA.

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Wikstrand, J., Berglund, G., Wilhelmsen, L., and Wallertin, I. (1978). Value of systolic and diastolic time intervals. *British Heart Journal*, **40**, 256-267.

This letter was shown to Dr Balasubramanian who replies as follows:

Sir,

We are grateful to Professor Spodick for drawing our attention to his views regarding correction of PEP for heart rate. This is controversial and it can hardly be said that there is a 'burgeoning' literature against correcting PEP for heart rate. Weissler *et al.* have always been advocating correction of PEP for heart rate and confirm it in all their recent reviews (Weissler *et al.*, 1968; Lewis *et al.*, 1974; Weissler, 1978); similarly, Salcedo and Siegel (1976) also advocate correction of PEP in their monograph on noninvasive cardiac diagnosis. They also point out that when atrial pacing is employed to increase the heart rate PEP does not shorten. Lewis and colleagues (1977) also advocate correction of PEP for heart rate. We, therefore, corrected PEP for heart rate as recommended by these workers.

We are fully aware of the pioneering contributions of Professor Spodick and his group in noninvasive cardiology for the past two decades, and have great esteem for him and his work. The 'misleadingly infelicitous turn of phrase' in citing Professor Spodick's work was totally unintentional.

V. Balasubramanian,
Cardiology Department,
Northwick Park Hospital and
Clinical Research Centre,
Watford Road,
Harrow,
Middlesex.

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British Heart Journal, 1979, **41**, 255

Effects of atrial fibrillation on prognosis of acute myocardial infarction

Sir,

In the above paper by Hunt, Sloman, and Penington (*British Heart Journal*, 1978, **40**, 303-307) the conclusion concerning the ominous prognostic import of atrial fibrillation as an intercurrent event in acute myocardial infarction comes as no surprise but certainly needed the documentation provided here. Apparently these patients were followed for at least 12 months, since the mortality rate is recorded at 3 and 12 months. However, while the short-term duration of atrial fibrillation was carefully documented, I could find no mention of the number who maintained atrial fibrillation as a dominant rhythm on a long-term basis or what—if any—attempts at conversion were instituted. Certainly this would be additional information of great importance to the clinician. Whether patients who had more than a single episode of transient atrial fibrillation or patients who had prolonged atrial fibrillation were kept on digitalis to ensure a modest ventricular response is also not mentioned. To the same end, the use of propranolol would bear discussion.

Their conclusions in terms of prognosis are, of course, interesting. The paper by Cristal *et al.* (1976) points out that atrial fibrillation in their studies had no effect on the prognosis of an inferior but did affect the prognosis of an anterior wall myocardial infarction. The studies of Liberthson *et al.* (1976), as well as a paper by Julian *et al.* (1964), seem to indicate that there is no particular difference in mortality related to the presence of atrial fibrillation—which certainly is at variance with this paper. Clinical observation certainly leads me, without statistical evidence, to be prejudiced in favour of the authors.

It would have been interesting, furthermore, if the premonitory events leading to the bouts of atrial fibrillation had been further discussed. The well-known factor of premature atrial cycles falling in the vulnerable period has been documented in the past and it might have been interesting to document this again.

Erich H. Loewy,
62 Elm Street,
Glens Falls, N.Y. 12801, USA.

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This letter was shown to Dr Hunt who replies as follows:

Sir,

Of the 77 patients who lived to 3 months, 6 remained in atrial fibrillation at that time, 3 of whom were known to be in chronic atrial fibrillation before their infarction. Attempts have not been made to revert the other 3 patients to sinus rhythm, but they were still receiving digitalis. We do not have data readily available to determine how many of the patients with transient or recurrent atrial fibrillation were receiving digitalis, but would estimate that at least half would be.

We do not have full data on the timing and frequency of atrial ectopic beats and to get these data would involve reviewing all the rhythm strips by hand. Certainly atrial ectopic beats were noted in 40 per cent of the patients who had atrial fibrillation and in 20 per cent of those in whom atrial fibrillation did not develop.

David Hunt,
Department of Cardiology,
The Royal Melbourne Hospital,
Parkville,
Victoria,
Australia.

Notices

British Heart Journal, 1979, **41**, 256

The Fourth World Conference on Smoking and Health

This conference will take place in Stockholm, Sweden, 18 to 21 June 1979. The conference will be organised by the Swedish Ministry of Health and Social Affairs together with the National Smoking and Health Association.

Particulars from Lars M. Ramström, Ph D, c/o RESO Congress Service, S-105 24 Stockholm, Sweden.

Non-invasive techniques in cardiology

The Third European Symposium of the British Heart Foundation on non-invasive techniques in cardiology will be held in Imperial College, South Kensington, London SW7 from 25 to 28 June 1979 and will be accompnaied by a trade exhibition. The main subjects under discussion will be: basic principles and traditional methods, echocardiography, nuclear cardiology, and electrocardiography.

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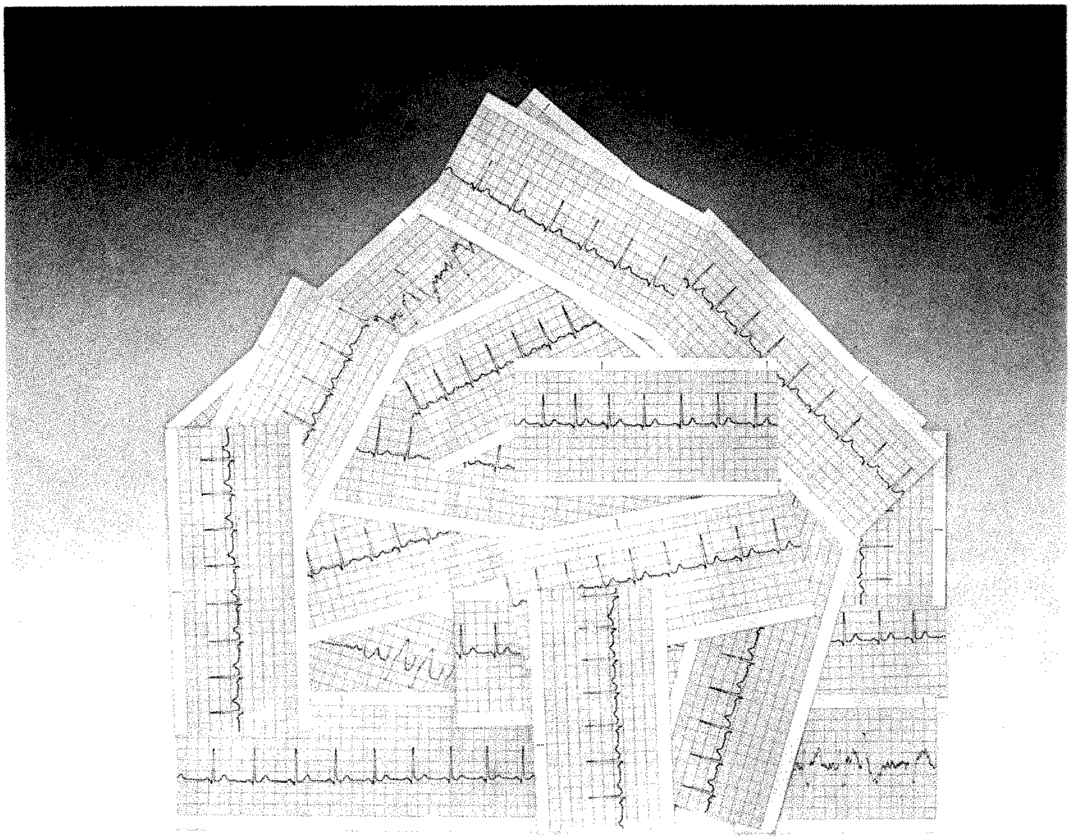
An International Congress on cardiac ischaemia and arrhythmias is to be held in Montreux, Switzerland, on 1-4 April 1979.

Further information can be obtained from Mr Michael Ferla, International Congress, P.O. Box 97, CH-1820 Montreux, Switzerland.



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March 1979 Vol 41 No 3

British Heart Journal

A monthly journal of cardiology published in association with the British Cardiac Society

Editorial: Thyroid heart disease *Cecil Symons* 257

Anatomy of left ventricular outflow tract *Robert Walmsley* 263

Coarctation, tubular hypoplasia, and the ductus arteriosus. Histological study of 35 specimens *S. Yen Ho and Robert H. Anderson* 268

Developmental anatomy of the membranous part of the ventricular septum in the human heart *S. P. Allwork and R. H. Anderson* 275

Morphological variations in pulmonary atresia with intact ventricular septum *James R. Zuberbuhler and Robert H. Anderson* 281

Conduction disturbances after surgical correction of ventricular septal defect by the atrial approach *Susan M. Hobbins, Teruo Izukawa, Dorothy J. Radford, William G. Williams, and George A. Trusler* 289

Open heart surgery in first year of life using profound hypothermia (core cooling) and circulatory arrest. Experience with 134 consecutive cases *Giuseppe Di Eusanio, Sadhan C. Ray, Raymund J. Donnelly, and David I. Hamilton* 294

Poor response to oral indomethacin therapy for persistent ductus arteriosus in very low birthweight infants *Richard W. I. Cooke and Douglas Pickering* 301

Failure of indomethacin to close persistent ductus arteriosus in infants weighing under 1000 grams *Hallam H. Ivey, John Kattwinkel, Tong S. Park, and L. Jerome Krovetz* 304

Arterial counterpulsation in severe refractory heart failure complicating acute myocardial infarction *Michael F. O'Rourke, Neville Sammel, and Victor P. Chang* 308

Comparative haemodynamic and peripheral vasodilator effects of oral and chewable isosorbide dinitrate in patients with refractory congestive cardiac failure *Jaime Figueras, William R. Taylor, Takeshi Ogawa, James S. Forrester, Bramah N. Singh, and H. J. C. Swan* 317

Study of left ventricular pressure-volume relations during nitroprusside infusion in human subjects without coronary artery disease *J. P. Merillon, G. Motte, M. C. Aumont, R. Prasquier, and R. Gourgon* 325

Blockade of cardiac and renal beta-receptors by low dose propranolol in normal subjects. Clues to its antihypertensive effect *Roy Davies, Thomas G. Pickering, Alberto Morganti, Maxim Wilson, and John H. Laragh* 331

Uptake of catecholamines by human cardiac muscle in vitro *M. C. Petch and W. G. Nayler* 336

Concentration of catecholamines in human cardiac muscle *M. C. Petch and W. G. Nayler* 340

Nongenetically transmitted disproportionate ventricular septal thickening associated with left ventricular outflow obstruction *Barry J. Maron, John S. Gottdiener, William C. Roberts, William J. Hammer, and Stephen E. Epstein* 345

Case reports

- Atrial infarction leading to rupture *N. Cristal, I. Peterburg, and I. Inbar-Yanai* 350
- Pulsus alternans induced by glyceryl trinitrate paste in a patient with alcoholic cardiomyopathy *P. A. N. Chandraratna, E. Langevin, and J. Langevin* 354

Correspondence 356

Proceedings of the British Cardiac Society 360

British Medical Association

ASTM CODEN: BHJUAV 41 (3) 257-384 (1979)

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Tissue Heart Valves

Edited by
Marian I. Ionescu, MD, FACS
Consultant Cardiothoracic Surgeon, The General Infirmary at Leeds
Clinical Lecturer in Cardiothoracic Surgery at Leeds University, Leeds, England

This is an up-to-date, comprehensive and authoritative work reviewing the clinical use of tissue heart valves. The editor, one of the pioneers in this field, has brought together a team of international authorities on heart valve replacement.

The early chapter on the Björk-Shiley prosthesis by Viking O. Björk is a standard against which the tissue valves can be measured. Tissue valves have an extremely low propensity for thromboembolism and can be used without long-term anticoagulant treatment. Their use in increasing numbers has established that the durability of the tissue valves is identical to that of prostheses for a similar length of follow-up. Also the hydraulic characteristics and the haemodynamic performance of most of the tissue valves are superior to their prosthetic counterparts. The tissue valves have proved a better alternative for heart valve replacement and they are now firmly established in the armoury of many cardiac surgeons. The clinical and laboratory results obtained with tissue valves are described, together with an *in vitro* evaluation of their function and the chemistry of their preservation.

Cardiac surgeons and cardiologists will find this book particularly valuable as will physicians, biomedical engineers and all serious students of heart valve disease and its surgical treatment.

1979   234 x 156 mm   394 pages   0 407 00139 5   £20.00   US $45.00

Contributors

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Contents

Prosthetic Heart Valve Replacement. Nine Years' Experience with the Björk-Shiley Tilting Disc Valve – Hydrodynamic Evaluation of Tissue Valves – Clinical and Experimental Comparison Establishing the Glutaraldehyde Treated Xenograft as the Standard for Tissue Heart Valve Replacement – Allograft and Autograft Valves used for Aortic Valve Replacement – The Glutaraldehyde-Stabilized Porcine Xenograft Valve – The Ionescu-Shiley Pericardial Xenograft Heart Valve – The Dura Mater Allograft Valve – The Use of Valved Conduits in the Surgical Treatment of Congenital Heart Disease – Right Ventricular Outflow Tract Reconstruction with Pericardial Monocusp Patch and Valved Conduit – The Chemistry and Biology of Aldehyde Treated Tissue Heart Valve Xenografts – Index

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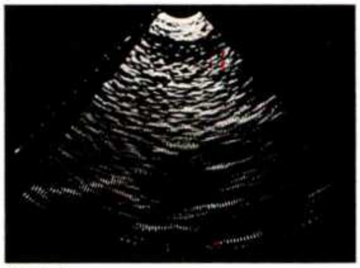

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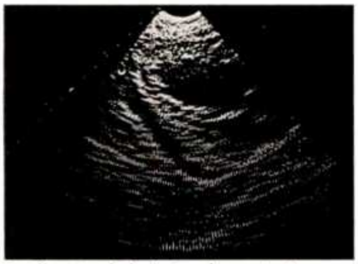

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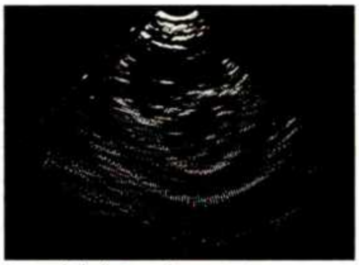

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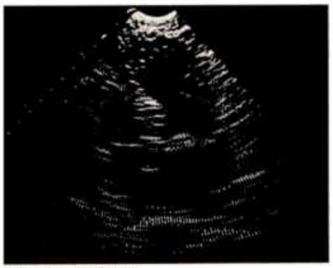
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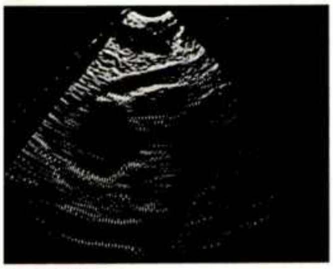
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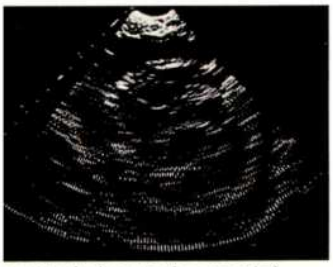
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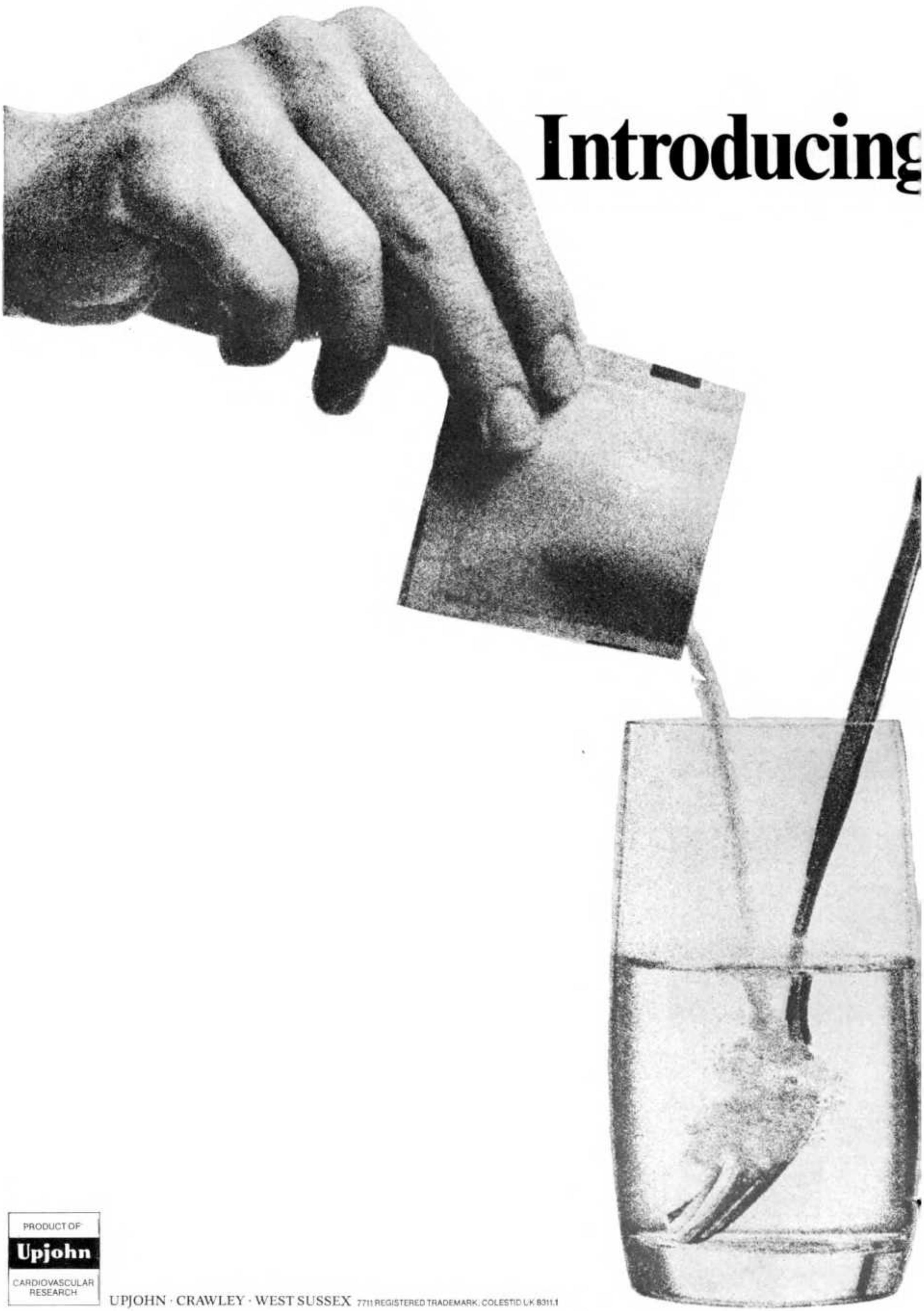

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[1] Meat Trades Journal 29.9.77

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VOL. 59 **JANUARY 1979** **NUMBER 1**

INTERNATIONAL LECTURE:

Effect of Cholesterol-Lowering Diet on Mortality from Coronary Heart Disease and Other Causes. Osmo Turpeinen 1

ORIGINAL ARTICLES:

Diabetes and Cardiovascular Risk Factors: The Framingham Study. William B. Kannel and D. L. McGee 7

Factors Contributing to Altered Left Ventricular Diastolic Properties During Angina Pectoris. Tift Mann, Sheldon Goldberg, Gilbert H. Mudge, Jr., and William Grossman 14

Influence of Right Ventricular Hemodynamics on Left Ventricular Diastolic Pressure-Volume Relations in Man. Philip A. Ludbrook, Joseph D. Byrne, and Robert C. McKnight 21

Editorial: Acute Displacement of the Diastolic Pressure-Volume Curve of the Left Ventricle: Role of the Pericardium and the Right Ventricle. John Ross, Jr. 32

Catecholamines in Coronary Sinus and Peripheral Plasma During Pacing-Induced Angina in Man. Leonard Schwartz, Michael J. Sole, Edward F. Vaughan-Neil, and Nasir M. Hussain 37

Myocardial Release of Lactate, Inosine and Hypoxanthine During Atrial Pacing and Exercise-Induced Angina. Gunther Kugler 43

Exercise Echocardiography: Detection of Wall Motion Abnormalities During Ischemia. Steven J. Mason, James L. Weiss, Myron L. Weisfeldt, John B. Garrison, and Nicholas J. Fortuin 50

Effects of Maximal Exercise Stress on Left Ventricular Function in Patients with Coronary Artery Disease Using First Pass Radionuclide Angiocardiography. A Rapid, Noninvasive Technique for Determining Ejection Fraction and Segmental Wall Motion. James A. Jengo, Victor Oren, Richard Conant, Marianne Brizendine, Thomas Nelson, J. Michael Uszler, and Ismae Mena 60

Improvement of Myocardial Perfusion and Left Ventricular Function After Coronary Artery Bypass Grafting in Patients with Unstable Angina. Albert J. Kolibash, John S. Goodenow, Charles A. Bush, Marc R. Tetalman, and Richard P. Lewis 66

Combined Aortic Valve Replacement and Myocardial Revascularization: Results in 220 Patients. James V. Richardson, Nicholas T. Kouchoukos, James O. Wright, III, and Robert B. Karp 75

The Effects of Ergonovine Maleate on Coronary Arterial Size. Paul R. Cipriano, Diana F. Guthaner, Arthur E. Orlick, Donald R. Ricci, Lewis Wexler, and James F. Silverman 82

Relationship of Cardiothoracic Ratio and Plain Film Heart Volume to Late Survival. K. E. Hammermeister, Paul M. Chikos, Lloyd Fisher, and Harold T. Dodge 88

Effect of Filming Projection and Interobserver Variability on Angiographic Biplane Left Ventricular Volume Determination. William J. Rogers, L. Richard Smith, William P. Hood, John A. Mantle, Charles E. Rackley, and Richard O. Russell 96

Spontaneous Course of ST Segment Elevation in Acute Anterior Myocardial Infarction. Rainer V. Essen, Wolfgang Merx, and Sven Effert 105

Enzymatic Indices of Myocardial Necrosis: Influence of Short- and Long-Term Prognosis After Myocardial Infarction. Peter L. Thompson, Edmund E. Fletcher, and Vi Katavatis 113

Cardiac Effects of Acute Ethanol Ingestion Unmasked by Automatic Blockade. John S. Child, Rodney B. Kovick, Jorge A. Levisman, and Morton L. Pearce 120

Prevalence and Characteristics of Disproportionate Ventricular Septal Thickening in Infants with Congenital Heart Disease. Barry J. Maron, Jesse E. Edwards, James H. Moller, and Stephen E. Epstein 126

Cross-Sectional Echocardiographic Diagnosis of Coronary Artery Aneurysms in Patients with the Mucocutaneous Lymph Node Syndrome. Junichi Yoshikawa, Koji Yanagihara, Takane Owaki, Hiroshi Kato, Yoshihiro Takagi, Fukumaru Okumachi, Takashi Fukaya, Yasuhiko Tomita, and Kinizo Baba 133

Real-Time Wide-Angle Sector Echocardiography: Atrioventricular Canal Defects. Donald J. Hagler, Abdul J. Tajik, James B. Seward, Douglas D. Mair, and Donald G. Ritter 140

Intraoperative Recording of Specialized Atrio-ventricular Conduction Tissue Electrograms in 47 Patients. Macdonald Dick, II, William I. Norwood, Carl Chipman, and Aldo R. Castaneda 150

Epicardial Activation of the Intact Human Heart Without Conduction Defects. Christopher R. Wyndham, Mooideen K. Meeran, Thomas Smith, Amarkanth Saxena, Richard M. Engelman, Sidney Levitsky, and Kenneth M. Rosen 161

Dilation of the Ductus Arteriosus by Prostaglandin E_1 in Aortic Arch Abnormalities. Michael A. Heymann, William Berman, Jr., Abraham Rudolph, and Victor Whitman 169

Anatomy of Aortic Atresia. Cases Presenting with a Ventricular Septal Defect. Gaetano Thiene, Vincenzo Gallucci, Fergus J. Macartney, Stefano Del Torso, Piero A. Pellegrino, and Robert H. Anderson 173

Morphological Development of the Pulmonary Vascular Bed in Experimental Pulmonic Stenosis. Daniel L. Levin, Michael A. Heymann, and Abraham M. Rudolph 179

Diagnostic Value of Visualization of the Right Ventricle Using Thallium-201 Myocardial Imaging. Fareed Khaia, Mohsin Alam, Sidney Goldstein, Daniel T. Anbe, and Daniel S. Marks 182

CASE REPORTS:

Skeletal Muscle Coronary Embolism: A Complication of Coronary Angiography. Malcolm M. McHenry and John Lee 189

LETTERS TO THE EDITOR 192

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Editorial

363/78

British Heart Journal, 1979, 41, 257-262

Thyroid heart disease

CECIL SYMONS[1]

The concept of thyrocardiac disease was introduced by Samuel Levine (Levine and Sturgis, 1924) who described atrial arrhythmias, congestive cardiac failure, and cardiac enlargement in hyperthyroidism occurring even in the absence of overt evidence of thyroid disorder. His clinical descriptions are as pertinent today as when they were written but it has always been a matter for conjecture whether thyroid disease in any of its forms can produce either specific pathological changes in the heart or an identifiable cardiac syndrome. The consensus from published work indicates that thyrocardiac disease as such is a clinical entity (Sandler and Wilson, 1959a; Staffurth and Morrison, 1968). Probably too much emphasis has been given to alterations in cardiac rhythm, a phenomenon symptomatic of associated muscle excitability. This survey discusses some of the experimental and clinical aspects of thyrocardiac disease and shows that a spectrum of response exists which may have a bearing on the nature of cardiomyopathy itself.

Action of thyroid hormones

The precise mode of action of thyroid hormones, thyroxine and tri-iodothyronine, is uncertain but contemporary view accepts that they have a direct inotropic and chronotropic effect on the heart. Much data have come from experimentally produced thyrotoxicosis and caution should be exercised in relating the results of animal experiments to the clinical situation in man, especially as the level of thyroxine dosage employed may exert effects at pharmacological and not physiological levels (Bernal and Refetoff, 1977). DeGroot (1972) has summarised the various ways the heart may be affected by thyroid hormones; the effects may be secondary to an increased cardiac output from a raised total body oxygen consumption, in turn the result of a direct action of thyroxine on mitochondrial oxidative phosphorylation, protein, and ribonucleic acid synthesis. Additionally adenylate cyclase activity may be altered and there may be an augmented response to catecholamines. There is now good evidence that the earliest action of thyroid hormones is to accelerate the basal respiratory rate of mitochondria (Hoch, 1967; Cohen, 1974). Experimentally, Zaimis *et al.* (1969) and Page and McCallister (1973) have shown that thyroxine greatly increases the number of mitochondria in the heart muscle cell and this change occurs before muscle hypertrophy. Hypertrophy has been described both in animals given thyroid hormones (Sandler and Wilson, 1959b; Cohen *et al.*, 1966) and in hyperthyroidism in man (Sandler and Wilson, 1959a).

Cellular activity is activated by adenylate cyclase which catalyses the production of cyclic 3′5′ AMP from ATP. Until recently it was thought that the positive inotropic and chronotropic effects on the heart produced by thyroid hormones were mediated in part by the action of catecholamines on the adenylate cyclase system. It now seems possible that there are separate adenylate cyclase systems for thyroid hormones and catecholamines (Levey and Epstein, 1969). Though it is accepted that in hyperthyroidism there is a normal sensitivity to circulating catecholamines, and plasma catecholamine levels are not increased (Stoffer *et al.*, 1973), the clinical picture presents as a summation effect of augmented adrenergic and thyroid responses. Buccino *et al.* (1967) have shown experimentally, in the isolated cat papillary muscle preparation, that the level of thyroid activity profoundly affects the intrinsic contractile state of cardiac muscle, independent of both noradrenaline stores and alterations in high energy phosphates. Beta-blockade reduces tachycardia and improves the general well-being of the hyperthyroid patient but does not reduce the excessive oxygen consumption (Howitt and Rowlands, 1967), return the heart rate to normal, or affect the underlying pre-ejection phase of cardiac contraction and duration of left ventricular systole (Pietras *et al.*, 1972). The role of calcium may be important, for the intrasarcomeric movement of this ion is intimately related to excitation-contraction coupling in cardiac muscle (Langer, 1968). Liu and Overman (1964) have shown that thyroxine increases the accumulation of intracellular calcium, and Nayler *et al.* (1971) showed that microsomes, prepared from the heart muscle of animals rendered hyperthyroid, accumulate and exchange calcium more readily than microsomes from euthyroid heart muscle.

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Clinical thyrocardiac disease

The prime haemodynamic change in hyperthyroidism is an increase in cardiac output, more so than is actually required to accommodate the rise in oxygen consumption (Kroetz *et al.*, 1962). The reason for the increased flow is obscure, but it is relevant that the heart has excessive work to perform arising from both increased preload caused by augmented peripheral flow, and by afterload resulting from the drive of thyroid hormones on the myocardial cell itself. The opposite prevails in hypothyroidism where even the low cardiac output is sufficient for the depressed metabolic requirements of the body. Essentially, thyroid hormones cause an unremitting positive inotropic and chronotropic effect on the heart in hyperthyroidism. In this respect, the circulatory changes arising in thyroid disease provide us with a useful model to indicate how any heart would respond over a prolonged time to near-maximal preload and afterload stimulation. We should be able to find examples of many forms of rhythm and heart muscle disorder arising from this form of stress and this appears to be the case. This hypothesis helps explain both the hyperkinetic circulatory response and the physical signs in the cardiovascular system, though persistent damage to the heart in any form of thyroid disorder can only be truly assessed when the endocrine condition has been fully treated. It also becomes simple to understand why, if some additional burden is present, as in mitral disease if a patient becomes hyperthyroid, severe circulatory changes manifest very quickly.

Clinically, the effects of thyroid hormones will be to produce changes in cardiac rhythmicity or of heart muscle function, or of both. There is little doubt that until recently, because of the dramatic effects on cardiac rhythm, the equally important underlying muscle changes have received insufficient attention. In hyperthyroidism, sinus tachycardia, ventricular ectopic beats (unifocal or multifocal), either singly or in salvoes, paroxysmal and then persistent atrial fibrillation, are common. There may be a specific predisposition to changes in atrial rhythm in thyroid disease. Five per cent of all clinically euthyroid patients with paroxysmal or permanent atrial arrhythmias were found to have underlying hyperthyroidism, as disclosed by routine laboratory screening procedures (Symons *et al.*, 1978). Wan *et al.* (1972) have described a high incidence of thyroid disorder in patients with sinuatrial disease. Instances of prolongation of the PR interval have been described (Hoffman and Lowrey, 1960) and the Wolff-Parkinson-White syndrome has been reported in thyrotoxicosis, with reversion to normal conduction after treatment of the thyroid condition (Strong, 1949; Sanghvi and Banerjee, 1961). Transitory and frequently florid inversion of T waves are commonly present in severe hyperthyroidism in younger patients and in the more acutely ill subject (Hoffman and Lowrey, 1960).

Most of the physical signs in hyperthyroidism other than those resulting from arrhythmias can be explained by the high output circulatory state. Vasodilatation and increased peripheral flow are manifest by warm extremities, a bounding pulse, and an easily visible jugular venous pulsation. Biventricular cardiac enlargement may be present, there is a snapping first heart sound, an apical third sound (or mid-diastolic flow murmur), or a basal systolic bruit, classically scratchy in character. An apical early peaking systolic murmur is occationally audible (Ueda *et al.*, 1963) and is probably the result of a muscle sound produced during the phase of powerful isovolumic contraction. In the older patient, signs may be minimal despite the increased cardiac output and the accent is more on chronic rhythm disturbance, that is atrial fibrillation. Cardiac failure, unusual today because of earlier diagnosis and an increased index of suspicion in unexplained cardiac disease, may be insidious in onset and high-output congestive in type, and is almost invariably accompanied by rapid atrial fibrillation. It is in these cases particularly that an underlying muscle problem must be sought, but both modern haemodynamic data and endomyocardial biopsy material are lacking in this form of thyrocardiac disease. Non-invasive techniques such as the estimation of systolic time intervals and left ventricular ejection times appear promising in the assessment of myocardial performance in thyroid disease (Parisi *et al.*, 1974; Burckhardt *et al.*, 1978).

Bradycardia with low voltage T waves in the electrocardiogram is common in hypothyroidism but occasionally the rate may be normal, and instances of arrhythmias which resolve, somewhat paradoxically, by treatment with thyroxine, have been reported (Ohler and Abramson, 1934; Hansen, 1961). Paroxysmal rapid arrhythmias also occur in patients with autoimmune thyroid disease, impaired thyroid reserve but normal serum levels of thyroxine (Symons *et al.*, 1978). Cardiac enlargement is usually the result of increased diastolic filling from bradycardia and, infrequently, caused by a large pericardial effusion. Minor degrees of effusion are common but are only detectable by echocardiography (Kerber and Sherman, 1975). Graettinger *et al.* (1958) found no haemodynamic evidence of cardiac failure in this condition and this accords with the rarity of failure and the generally complete resolution of physical signs on adequate treatment with thyroxine. Much debated is the role of atherosclerosis in hypothyroidism. Steinberg (1968) in a necropsy study of myxoedema found that coronary disease was more obvious only when hypertension had been present in life. Vanhaelst *et al.* (1967) failed to observe any increased frequency of occurrence of myocardial infarction in untreated or in inadequately treated patients with thyroid failure, though they reported an increase in incidence in coronary artery disease in these cases. The association of a raised serum cholesterol level in patients who are euthyroid but who have positive thyroid antibodies has been described by Bastenie *et al.* (1967) and Fowler and Swale (1967). It is claimed that recognition and treatment with thyroxine of this form of subclinical hypothyroidism or 'premyxoedema' may prevent progression to atherosclerotic disease (Fowler *et al.*, 1970). This is still a contentious matter, for thyroid disease is predominantly a disorder affecting women while coronary heart disease is much more common in men. Tunbridge *et al.* (1977) in an extensive survey of a mixed urban and rural population concluded that there was no association between cholesterol or triglyceride levels and thyroid antibodies or thyroid stimulating hormone (TSH) and that any relation between ischaemic heart disease and minor degrees of thyroid failure was unlikely to be mediated by lipid abnormalities. Symons *et al.* (1978) have not recorded a raised cholesterol or a propensity to coronary artery disease in patients with subclinical hypothyroidism, and they suggest either a cardiomyopathic response resulting from autoimmune disease or adverse effects on the myocardium of circulating analogues of thyroid hormones.

Cardiomyopathy and thyroid disease

Considerable clinical variation exists in the manner in which thyroid hormones affect the heart and circulation. Generally the non-cardiac element of the endocrine disorder will overshadow symptoms and signs, and little notice is (or need be) taken of the cardiovascular status, which will return to normal once treatment of the thyroid condition is effected. An entirely different situation is extant in the older subject who is less likely to show evidence of thyroid disease though the underlying metabolic disturbance is still pronounced. Thyroid disease as the precipitating cause of arrhythmias, cardiac failure, and even angina pectoris may go unrecognised for many years before hyperthyroidism is diagnosed (Somerville and Levine, 1950), and it is this form of hidden thyroid disorder, both under- and over-activity, which may be responsible for prolonged cardiac invalidism. Appropriate treatment then clearly indicates the endocrine basis of the hitherto idiopathic nature of the cardiac condition. Occasionally with the return of the euthyroid state it is evident that some form of heart muscle disease is present, especially if atrial fibrillation remains or recurs after DC reversion. Congestive cardiomyopathy caused by previous thyroid disease becomes the only possible diagnosis. An indication that cardiomyopathy may be allied to metabolic disorder is suggested from the work of Resnekov and Falicov (1977) who described patients with hyperthyroidism and lactate-producing angina pectoris but with normal coronary vessels as assessed by cineangiography. The clinical findings related to the experimental findings become even more complex and concern the role of analogues of triiodothyronine and thyroxine, triac and tetrac, respectively. These substances appear to have a direct action on heart muscle by increasing cellular respiration with only a marginal increase in the overall metabolic rate (Barker and Lewis, 1956; Lerman, 1961). In 1971, Symons *et al.* reported the presence of circulating triac and tetrac in a euthyroid patient with heart disease who later became hyperthyroid. Because of this and because longstanding thyroid disease had been reported in patients with hypertrophic cardiomyopathy (Symons *et al.*, 1974), a series of experiments was designed using carefully titrated doses of thyroid hormones to simulate longstanding covert hyperthyroidism and to study the effect on the myocardium. In the first experiment (Symons *et al.*, 1975) hypertrophy was produced in the heart of young adult rats, more so by triac than by thyroxine; in the second study gross changes of muscle fibre disarray at subcellular level, comparable with that seen in hypertrophic cardiomyopathy in man, were produced in the fetal but not the maternal heart when triac was given to pregnant rats (Olsen *et al.*, 1977). Propranolol prevented the production of disarray but not the changes of simple hypertrophy (Olsen *et al.*, 1978), and this finding may again revive earlier hypotheses that the circulatory manifestations of hyperthyroidism are mediated through the sympatho-adrenomedullary system (Brewster *et al.*, 1956). Equally interesting possibilities merit consideration. Is hypertrophic cardiomyopathy an endocrine disorder, possibly caused or accentuated in fetal life by some alteration in thyroid metabolism? This is of particular interest, for experimentally the placenta is relatively impermeable to thyroxine, tri-iodothyronine, and TSH (Fisher, 1975). Does a hyperkinetic or hypertrophic circulatory state precede obstructive hypertrophic changes as Perloff (1971) and Williams *et al.* (1973) have suggested? Is this change initiated in fetal life during rapid development when the heart muscle may be vulnerable to any physiological or pathological stimuli having inotropic and chronotropic effects? Bulkley *et al.* (1977) have shown that disarray of myocardial fibres is relatively common in some forms of congenital heart disease. Another possibility is that analogues of thyroxine and tri-iodothyronine are present in the circulation in adult life and, because of minimal evidence of overall metabolic disturbance, are able to cause underlying heart muscle disease. Further work is required to determine the respective role of catecholamines and thyroid hormones in producing hypertrophic cardiomyopathy and the related changes of gross muscle disarray. Clinically, in patients with heart disease, a reliable method of estimation of circulating analogues of thyroid hormones is needed.

Treatment

It is not the purpose of this review to discuss in detail the modes of clinical presentation of thyroid heart disease. Unexplained cardiac symptoms or signs in any patient with or without heart disease should lead to a request for laboratory assessment of thyroid status, especially a serum thyroxine estimation, thyroid antibodies, and ideally TSH levels after thyrotrophin-releasing hormone stimulation. A biochemical diagnosis of hyper- or hypothyroidism, despite the absence of clinical evidence of thyroid disease, should lead to effective treatment and may result in impressive recovery, especially in the older subject who has suffered prolonged cardiac ill health. Indeed there is much to commend a serum thyroxine estimation as a routine screening procedure in all patients in the latter half of life with cardiac disability.

Knowing the excessive systemic overload caused by hyperthyroidism on the one hand and cellular depression produced by hypothyroidism on the other, the various forms of treatment that are available can be rationalised. A remarkable advance in the treatment of hyperthyroidism occurred with the advent of beta-blocking drugs which competitively inhibit the action of catecholamines at the beta-adrenergic receptor sites. Propranolol is still the best of these compounds and has immediate effect in reducing anxiety, tremor, and tachycardia, and does much to bring the acute manifestations of thyrotoxicosis under control. Nevertheless it does not alter the underlying thyrotoxic disorder, and carbimazole, thyroid surgery, or radioiodine treatment will still be required as definitive treatment in the majority of cases. Too large a dose of propranolol in the acute state is unnecessary and can occasionally be harmful since the metabolic action of thyroxine is unaffected and the negative inotropic and chronotropic effects of beta-blockers on the heart could compromise myocardial function. Digoxin and diuretic treatment is indicated in the high output cardiac failure state with atrial fibrillation caused by hyperthyroidism. The serum levels of digoxin are low in thyroid overactivity, principally because of increased renal excretion (Croxson and Ibbertson, 1975), and larger doses than usual are required which should be given after estimating serum levels. It is important to realise that cardiac glycosides will still augment contractility of cardiac muscle to the same maximum as that observed in the euthyroid state (Buccino *et al.*, 1967). Occasionally propranolol is indicated with digoxin and diuretics, even in the presence of cardiac failure, to combat otherwise uncontrollable atrial fibrillation. In younger patients atrial fibrillation will usually revert to sinus rhythm when the euthyroid rate is attained, but in the older subject this may not be the case and DC reversion is indicated. Most are reverted and remain in sinus rhythm, but if the arrhythmia persists or returns then it is possible that cardiomyopathy is present. Congestive cardiomyopathy is treated in the usual way with digoxin and diuretics, as antithyroid treatment has already been used. Stafforth *et al.* (1977) have reported frequent episodes of arterial embolism in their patients with thyrotoxicosis and atrial fibrillation, and for whom they recommend anticoagulation if under the age of 65 years. Hypertrophic cardiomyopathy can only be regarded at present as an incidental and additional form of cardiac disorder occasionally occurring with hyperthyroidism, though Bell *et al.* (1978) report a high incidence of hyperthyroidism in patients with hypertrophic disease. Propranolol is still the best form of treatment for this condition.

In myxoedema the cautious institution of thyroxine therapy is essential for, though failure is rarely present in the florid state, the capacity of the heart to respond to increased peripheral demand is limited and left ventricular failure may be precipitated. Pericardial effusion as shown by echocardiography may take some time to disappear but it is only infrequently of clinical significance. It is not yet known whether treatment for premyxoedema will prevent overt disease or if it delays progression of atherosclerosis.

To think of thyroid disorder as a possible cause of illness in a patient with heart disease, be it an unexplained arrhythmia or some form of cardiomyopathy, is to request a laboratory profile of thyroid function tests. The measure of improvement that can be obtained by appropriate treatment is satisfactory not only to the patient but to the cardiologist who realises that covert thyroid disease is often clinically undiagnosable. It is salutary to reflect that in 1936 Levine wrote of thyroid heart disease as, 'probably the most important aspect of all heart disease for it comprises the one large group of cases in which the difference between accurate and inaccurate diagnosis and treatment is the difference between chronic invalidism or death and restoration of health and life'. Methods of diagnosis and treatment have improved almost beyond measure since this statement was made, but awareness that thyroid disease may be present as an associated cause of cardiac ill health is still not fully recognised.

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Anatomy of left ventricular outflow tract[1]

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SUMMARY The left ventricular outflow tract is here considered to be that region of the left ventricle that lies between the anterior cusp of the mitral valve and the ventricular septum. The ventricular septum lies at an angle of 45 degrees to the median plane. The 'anterior' wall of the outflow tract is therefore anteromedial and the 'posterior' wall is posterolateral.

In the anterior wall are both the muscular and membranous parts of the ventricular septum. The outflow septal myocardium is smooth-walled. At the junction of the muscular and membranous parts of the septum lies the atrioventricular bundle. The right face of the membranous septum gives attachment to the medial wall of the right atrium and also to a small part of the septal cusp of the tricuspid valve. The membranous septum is therefore partly atrioventricular. At its upper end the membranous septum is continuous with the right lateral wall of the root of the aorta. The root of the aorta passes to the right and upwards and the membranous septum separates the aorta from the right ventricle.

The posterior wall of the outflow tract is formed not only by the anterior mitral cusp but also by the 'intervalvar septum' and, in its upper part, by a curtain formed by the fusion of the anterior and posterior mitral cusps.

The ventricular septum, like the atrial septum, lies at an angle of about 45 degrees to the median plane. The septa are so orientated that the right heart lies as much in front of the left heart as to its right side. The entire length of the inflow tract of the left ventricle may be seen in sections of the entire thorax that pass parallel to the ventricular septum. To prepare sections to show the length of the left ventricular outflow tract the heart must, however, be cut vertically at right angles to the ventricular septum (Fig. 1). In such sections the ventricular septum is seen to form the anteromedial wall of the outflow tract: for simplicity in nomenclature this will be called its 'anterior' wall. The greater part of the posterolateral wall of the tract is formed by the anterior (aortic) cusp of the mitral valve: again, for the sake of simplicity, this will be called the 'posterior' wall. This outflow tract region of the left ventricle has been called the aortic vestibule, and the subaortic, subvalvar, or subvalvular region by different workers. Though the outflow tract of the left ventricle might justifiably be regarded as extending from the left ventricular apex to the aortic valve I shall here consider the left ventricular outflow tract to be that part of the left ventricular chamber that lies in front of the anterior cusp of the mitral valve.

According to such a definition of the left ventricular outflow tract it must be emphasised that there is no line of demarcation on its anterior (septal) wall to indicate the lower border of the tract. This is indicated on its posterior wall by the free lower border of the anterior cusp of the mitral valve, a uniquely important structure in cardiac anatomy. The anterior mitral cusp is interposed between the inflow and outflow tracts of the left ventricle: the inflow tract lies below and behind the cusp and the outflow tract is in front of it. The left ventricular outflow tract is a complex musculomembranous channel or tunnel which has a length of about 25 mm in the adult heart: its length does, however, show considerable variation in different hearts.

Anterior wall of left ventricular outflow tract

The anterior wall of the outflow tract is formed by the obliquely orientated ventricular septum. Though the greater part of this wall is formed by the muscular part of the septum, its upper medial

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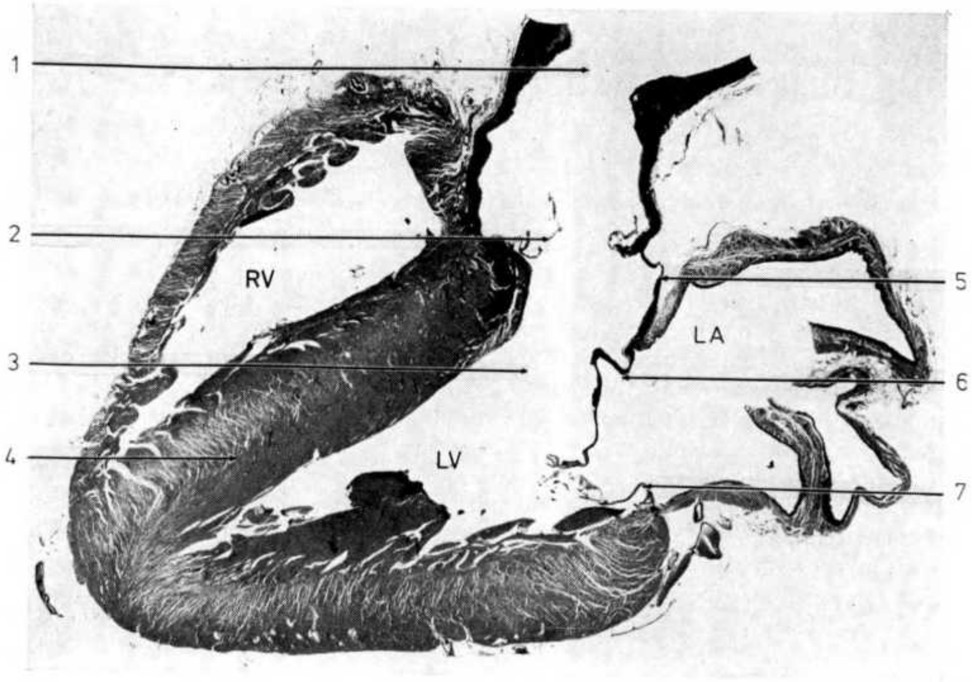

Fig. 1 *Section through the heart of a 50-year-old man, to show both the inflow and outflow tracts of left ventricle. The outflow tract of the left ventricle lies in front of the anterior cusp of the mitral valve. The intervalvar septum is unusually long in this heart. The left atrium (LA) is seen to lie behind the left ventricle (LV) and the right ventricle (RV) lies above and in front of the ventricular septum in this oblique section. (1) ascending aorta; (2) right coronary cusp of aortic valve; (3) left ventricular outflow tract; (4) ventricular septum; (5) intervalvar septum; (6) anterior cusp of mitral valve; (7) posterior cusp of mitral valve.*

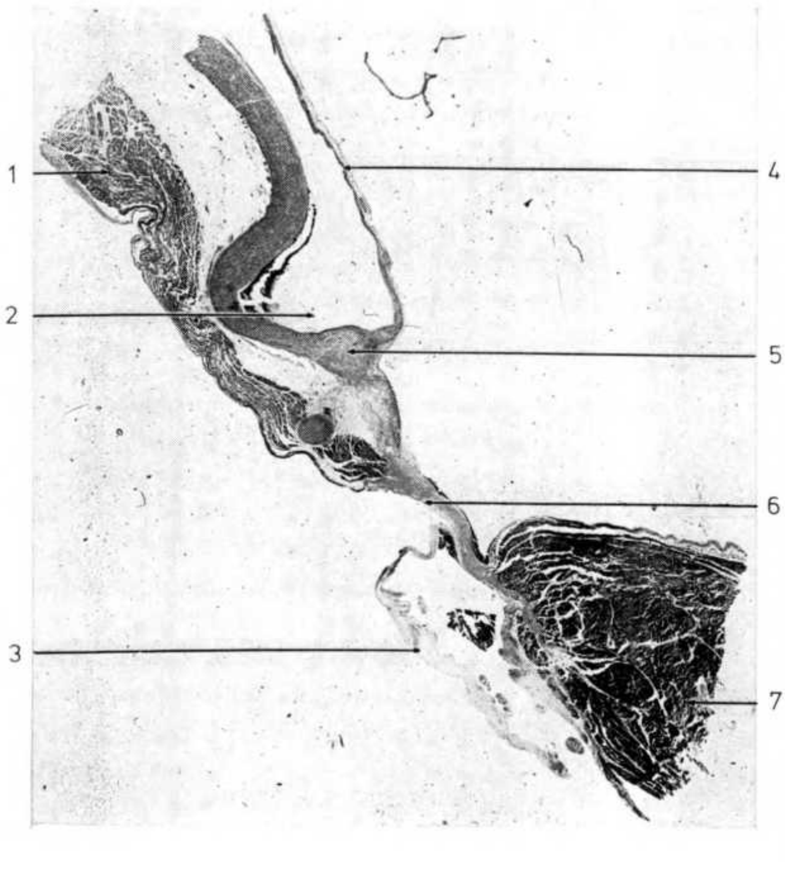

Fig. 2 *Section through the right lateral wall of the root of the aorta and membranous and muscular parts of ventricular septum. The septal cusp of the tricuspid valve and the medial wall of the right atrium are attached to the right face of the membranous septum which is orientated obliquely at an angle of about 45 degrees to median plane. (1) Medial wall of right atrium; (2) right coronary aortic sinus; (3) septal cusp of tricuspid valve; (4) right coronary cusp of aortic valve; (5) aortic annulus; (6) membranous septum; (7) muscular ventricular septum.*

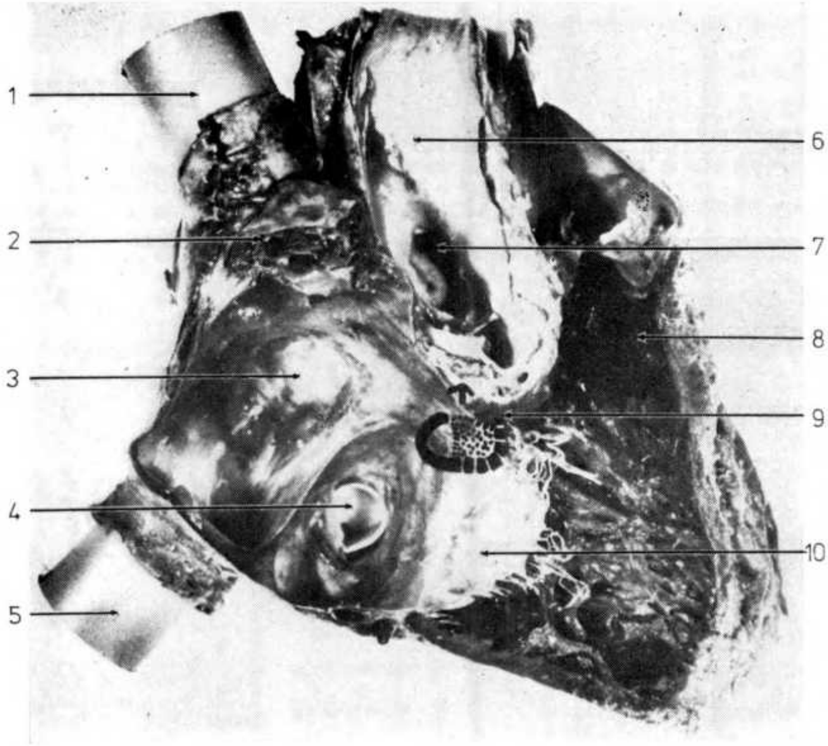

Fig. 3 *Section of right heart to show the medial septal wall of the right atrium and the right ventricle. Plastic tubes were inserted into the superior and inferior venae cavae. The septal cusp of the triscupid valve is seen in its entirety. The region of the membranous septum is indicated by continuous and interrupted lines. The interrupted line and stippled area show the part of the membranous septum that is under cover of the triscupid valve cusp. The arrow indicates the junction of the right coronary and non-coronary cusps of the aortic valve.* (*1*) *Superior vena cava;* (*2*) *right atrial appendage;* (*3*) *fossa ovalis, right atrium;* (*4*) *coronary sinus ostium;* (*5*) *inferior vena cava;* (*6*) *aorta;* (*7*) *left coronary artery ostium;* (*8*) *infundibulum, right ventricle;* (*9*) *supra-ventricular crest;* (*10*) *septal cusp of tricuspid valve.*

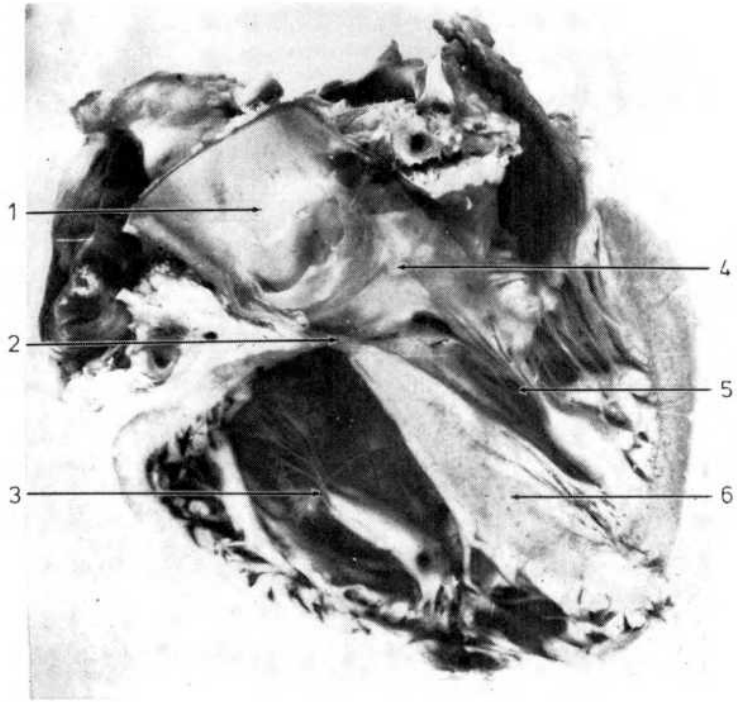

Fig. 4 *Oblique section of the heart to show both right and left ventricles and lower part of the ascending aorta. The right lateral wall of the aorta passes downwards and to the left to become continuous with the membranous part of the ventricular septum which overlies the right ventricle.* (*1*) *Ascending aorta;* (*2*) *membranous part of ventricular septum;* (*3*) *right ventricle;* (*4*) *anterior cusp of mitral valve;* (*5*) *left ventricle;* (*6*) *muscular ventricular septum.*

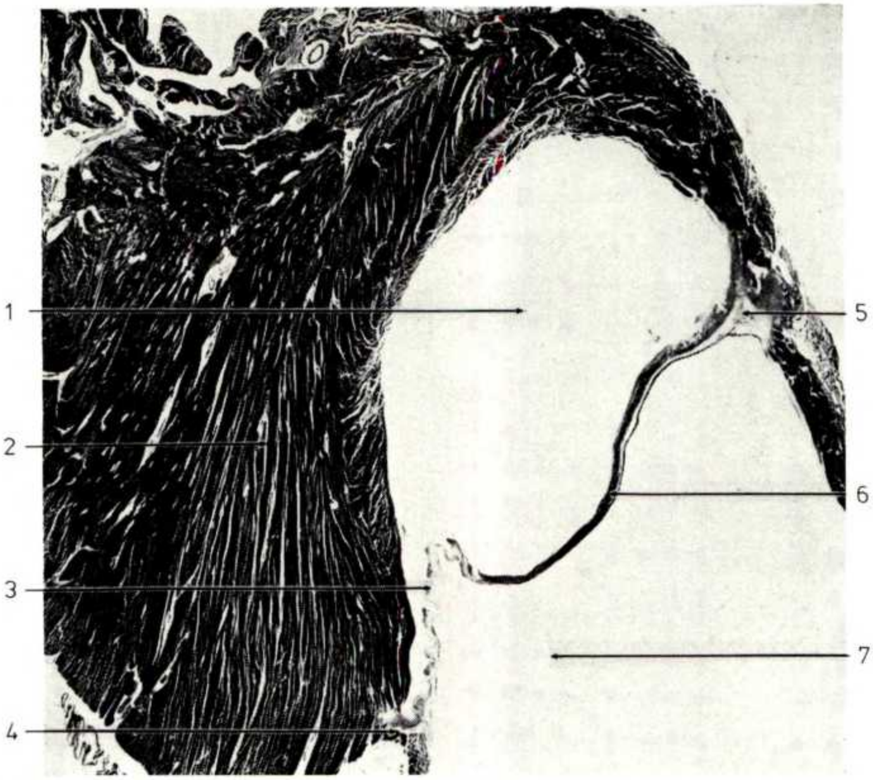

Fig. 5 *Transverse section of the upper part of the left ventricular outflow tract. It shows the curtain or veil that is formed by the fusion of the anterior and posterior (lightly stained) mitral valve cusps. This cuspal curtain forms the posterior wall of the tract in its uppermost part. (1) Left ventricular outflow tract; (2) myocardium of left ventricle; (3) posterior cusp of mitral valve; (4) mitral fibrous 'ring'; (5) central fibrous body; (6) anterior cusp of mitral valve; (7) left atrium.*

part is formed by the membranous ventricular septum.

The myocardium of the anterior wall is characterised by the smoothness of its free surface: in none of many normal human hearts examined has there been any evidence of the trabeculae carneae that are such a prominent feature of the inflow tract of the ventricle. It is to the uppermost part of this septal myocardium that part of the right coronary cusp of the aortic valve is attached (Fig. 1). In many normal hearts examined it is the same myocardium that protrudes so obviously into the immediate subaortic part of the outflow tract. Hypertrophy of this myocardium would certainly cause a narrowing of the outflow tract.

The membranous part of the ventricular septum has a maximum breadth of 15 mm in the hearts I have examined histologically and measures about 10 mm from the aortic annulus to the muscular septum (Fig. 2): it is about 1 mm thick.

Two structures, namely the septal cusp of the tricuspid valve and the medial wall of the right atrium, gain attachment to the right face of the membranous septum (Fig. 2). The manner of attachment of these 2 structures results in the membranous septum separating the left ventricle not only from the right ventricle but also from the right atrium. (It also separates the left ventricle from the pericardial cavity.)

It is a simple matter to make a section through the entire right heart to show both the inflow and outflow tracts of the right ventricle which lie parallel to the ventricular septum (Fig. 3). The septal cusp of the tricuspid valve is usually found to be closely applied to the ventricular septum as it would be in ventricular diastole. As viewed from the right ventricle the membranous septum lies below the posterior part of the supraventricular crest on the upper surface of which nestles the root of the aorta. Within the root of the aorta are the 3 dilatations of the aortic sinuses of Valsalva. The junctional zone between the right coronary and noncoronary cusps of the aortic valve lies above the membranous septum.

It is an anatomical fact that the ostium of the left coronary artery, when it is 'on centre' at the middle of the left coronary sinus, lies diametrically opposite the junction of the right coronary and noncoronary cusps: it is, however, at least 25 mm above the cuspal junction. Thus, the upper surface of the closed aortic valve is directed not only upwards but also to the right (Fig. 4).

At the lower part of the junction of the membranous and muscular parts of the ventricular septum lies the atrioventricular bundle of His. Developmentally and anatomically the main His bundle is primarily associated with the myocardium of the septum and through its right and left bundle-branches it supplies the entire musculature of the ventricles. The membranous septum is complex in its development and it is not surprising that a failure in its formation is so frequently a feature of many malformed hearts. In this connection it is important to note that, in the normal heart, the membranous ventricular septum is continuous, through the aortic annulus, with the right lateral or inferior wall of the root of the ascending aorta (Fig. 2).

The obliquity of the root of the aorta is a fact of major anatomical importance. It passes upwards and to the right at an angle of at least 45 degrees to the median plane. The right aortic wall, in the region of the noncoronary sinus, impinges on the anterior part of the medial wall of the right atrium to form the interatrial eminence called the torus aorticus. The membranous septum has, *in situ*, an orientation that is even more nearly horizontal than the right wall of the aortic root (Fig. 4). As the aorta overlies the right ventricle it would not require any dextroposition of its root for it to communicate with the right ventricle if there were a failure in development of the membranous septum.

In an enlarged heart with mitral stenosis and calcification of the 'appositional zones' (Walmsley, 1978) of both mitral cusps the membranous septum was found to be paper-thin.

Posterior wall of left ventricular outflow tract

The greater part of the posterior wall of the outflow tract is formed by the anterior cusp of the mitral valve.

In the human heart the line of attachment of the anterior wall of the left atrium is below the attachment of the left coronary cusp of the aortic valve (Fig. 1). The intervening space is bridged by a fibrous lamina which has been called the 'intervalvar septum' (Walmsley and Watson, 1978). This septum, which varies between 2 and 10 mm in length in the adult human heart, also participates in the formation of the posterior wall of the outflow tract.

A second additional structure in the posterior wall of the outflow tract is the posterior (mural) mitral cusp. It is well recognised that the cusps of both atrioventricular valves fuse with one another in their basal parts for most of 1 cm. The uppermost part of the posterior wall of the outflow tract is formed, therefore, by a curtain or veil of the fused mitral cusps (Fig. 5). The posterior mitral cusp component of this curtain is easily identified by the notched appearance of its ventricular surface, resulting from the attachments of chordae tendineae of the third order: in microscopical sections it stains lightly. At its lateral or basal side this posterior cusp is attached to the relatively narrow atrioventricular fibrous 'ring' which lies in the depth of the atrioventricular sulcus. On the medial or right side the anterior mitral cusp is attached to the central fibrous body, as it is always seen to be in transverse sections of the heart at this level. It is in sections such as this that the left ventricular outflow tract truly has the appearance of a musculomembranous tunnel.

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Coarctation, tubular hypoplasia, and the ductus arteriosus

Histological study of 35 specimens[1]

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SUMMARY A histological study has been made in an attempt to study further the relation between the ductus arteriosus, coarctation, and tubular hypoplasia of the aortic arch. Thirty-five aortic arch systems were studied using serial sectioning techniques. Twelve were from patients with coarctation and/or tubular hypoplasia. The other 23 hearts were from patients without aortic obstructive lesions, 7 from anatomically normal hearts, and the others from malformed hearts with anomalies elsewhere from the aortic arch. The anatomical study of the hearts with obstructive aortic lesions emphasised the necessity of distinguishing 'coarctation' from 'tubular hypoplasia', since the curtain lesion of coarctation was found to coexist with tubular hypoplasia in some cases. The histological study showed that the ductus was easily distinguished from the walls of the aorta or pulmonary artery. In all these cases with coarctation or tubular hypoplasia a sling of ductal tissue was located around the aortic isthmal orifice. In 6 hearts a diaphragm of ductal tissue was seen to form the coarctation lesion.

'Coarctation' is derived from the Latin word 'coarctatio' which means (a drawing together to make tight). When applied to the aortic arch, this term refers to an abrupt constriction situated in the aortic isthmus between the origin of the left subclavian artery proximally and the aorta-ductus arteriosus junction distally. This isthmic coarctation involves an obliterative or obstructive curtain lesion, the aetiology of which is still in dispute (Krediet, 1965; Balis *et al.*, 1967; Wielenga and Dankmeijer, 1968; Hutchins, 1971; Bruins, 1973; Rosenberg, 1973).

Another lesion which produces restriction of aortic flow in this region is tubular or isthmal hypoplasia. This lesion may or may not accompany a curtain lesion. Indeed, Sinha *et al.* (1969) proposed a radiographic definition of tubular hypoplasia as distinct from coarctation. Bremer (1948) considered this lesion to be the persistence of the fetal configuration of the aortic isthmus. Though a gradual narrowing of the aortic isthmus is a normal finding in the first 3 months of life (Evans, 1964), persistence of this stricture in later life is pathological.

Although the coarctation lesion is generally located in the region of the isthmus, there is much contention in its classification. Indeed, one of the first attempts at classification was that by Bonnet in 1903 which has become a classical reference. Since then many workers have found the simple classification into infantile and adult types inadequate (Evans, 1933; Bramwell, 1947; Edwards *et al.*, 1948; Johnson *et al.*, 1951; Clagett *et al.*, 1954; Lemmon and Bailey, 1958; Rudolph *et al.*, 1972). Becker *et al.* (1970) generalised that coarctation occupied the area of junction between the arch and descending aorta. The lesion could be proximal to, opposite to, or distal to the ductus arteriosus. Rudolph *et al.* (1972) introduced the term 'juxtaductal' coarctation and this term has since been used by other workers (Shinebourne and Elseed, 1974; Elseed *et al.*, 1974).

In the present study we have studied the anatomy of coarctation and attempted to define its relation to tubular hypoplasia and the ductus arteriosus.

Materials and methods

Thirty-five specimens were obtained from the cardiopathological collection of the Brompton Hospital, London, and the Wilhelmina Gasthuis, University of Amsterdam. Segments of aortic

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Table *Morphology of 12 hearts with tubular hypoplasia and/or coarctation of aortic arch*

Diagnoses *Situs—AV connection—VA connection*	*Aortic stenosis or obstruction*	*Associated anomalies*	*External localised aortic stricture*	*Obstructive coarctation lesion*
Solitus—AV concordance—VA concordance	+	Mitral atresia, hypoplastic LV, VSD, muscular subaortic stenosis, PDA	–	–
Solitus—AV concordance—VA concordance	+	Mitral stenosis, aortic atresia, hypoplastic LV, PDA	–	–
Solitus—AV concordance—VA concordance	+	Mitral stenosis, aortic atresia, hypoplastic LV, PDA	–	–
Solitus—AV concordance—VA concordance	+	Mitral stenosis, fibromuscular subaortic stenosis, bicuspid aortic valve, hypoplastic LV, PDA	–	+
Solitus—AV concordance—VA concordance	+	ASD, membranous subaortic stenosis, VSD, PDA	+	+
Solitus—absent right AV connection—VA concordance	+	Univentricular heart, LV type with OC, PDA	–	–
Solitus—absent right AV connection—VA discordance	+	Univentricular heart, LV type with OC, PDA	–	–
Solitus—absent left AV connection—VA discordance	+	Univentricular heart, LV type with OC, PDA	–	+
Solitus—AV concordance—DORV	+	ASD, VSD, PDA	–	+
Solitus—AV concordance—VA discordance	+	VSD	+	+
Solitus—AV concordance—VA discordance	+	VSD (AV canal type), PDA	–	+
Solitus—AV concordance—VA concordance	+	Anomalous pulmonary venous return, common atrium, PDA	–	–

ASD, atrial septal defect; AV, atrioventricular; DORV, double outlet right ventricle; LV, left ventricle; OC, outlet chamber; PDA, persistent ductus arteriosus; VA, ventriculoarterial; VSD, ventricular septal defect.

arches which included the ductus arteriosus and portions of the pulmonary artery were resected and studied histologically. Measurements were made of all the specimens and each one was drawn to scale. Seven of the arches were from anatomically normal hearts, and 28 from congenitally malformed hearts of which 12 were associated with coarctation and/or tubular hypoplasia.

Twenty-one specimens were sectioned in a plane parallel to the longitudinal axis of the arch, 5 in the sagittal plane of the ductus, and 9 transversely. The ribbons of serial sections were collected on cardboard trays. Initially, every twenty-fifth section was mounted and stained with the modified Masson's trichrome technique (Smith *et al.*, 1977). Where necessary, additional sections were later stained in haematoxylin and eosin or Verhoeff's van Gieson.

Results

(i) NORMALS

(This includes the 'normal-looking' arches from congenitally malformed hearts. The term 'normal-looking' is used in this study to refer to those arches without distinctly perceptible external strictures. Right sided aortic arches and discordant ventriculoarterial connections may also be covered by this term.)

The 7 specimens from anatomically normal hearts were newborn (3 specimens), 1 day old (2 specimens), 3 days old (1 specimen), and 6 days old (1 specimen). The ductus arteriosus was probe patent in all cases except for the 3-day-old specimen. The isthmal region in each case was slightly narrower than either the ascending or descending aorta but no plication was observed (Fig. 1).

The other 16 normal-looking arches were from congenitally malformed hearts. Five of those were associated with non-patent ductus and the age range was 3 days to 2¼ years. The rest ranged from 1 day to 6 months old. From an histological standpoint, the aorta, being one of the great arteries, had the characteristic appearance of regularly spaced elastic lamellae in the media. The isthmus had a similar histological structure to the rest of the aorta though the elastic lamellae were more condensed, giving it a slightly thinner wall. As in the great arteries, the ductal wall was made up of three layers—the intima,

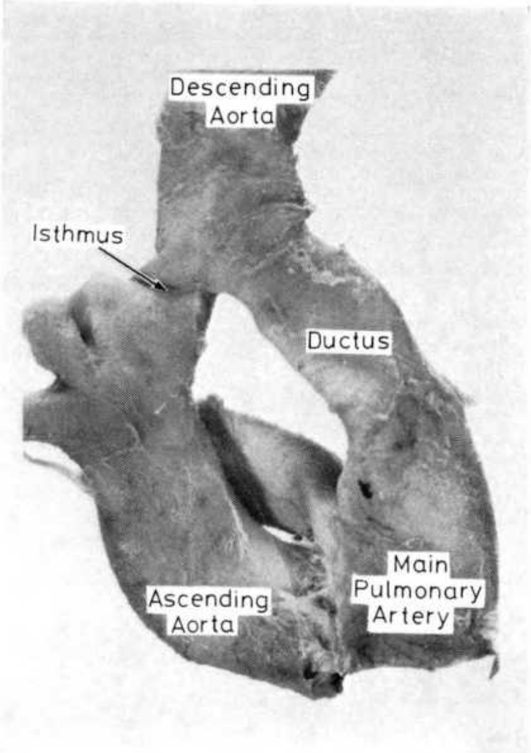
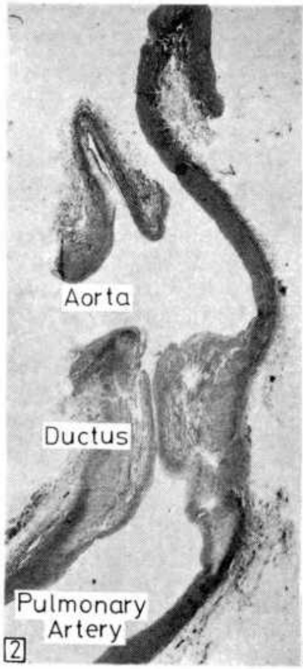


Fig. 1 *Normal aortic arch from a newborn infant. The isthmus is slightly narrower than either the ascending or descending aorta.*



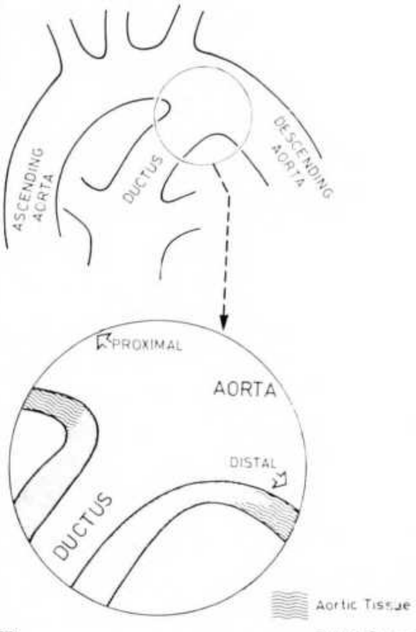


Fig. 2 *Longitudinal section of a normal obliterating ductus. Histologically, the ductus lacks the regularly spaced elastic lamellae of either the aorta or pulmonary artery. (Trichrome.* × *8.)*

Fig. 3 *Diagram of aortic arch and ductus with inset to show the ductus-aorta junction.*

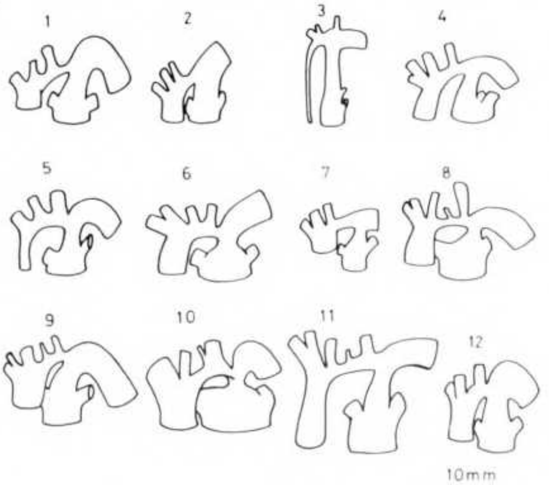


Fig. 4 *Scale diagram of the 12 coarctation and/or tubular hypoplasia specimens sectioned.*

media, and adventitia. However, in contrast to the aorta, the ductus lacked the regularly spaced elastic lamellae of the great arteries, being essentially a muscular artery (Fig. 2). The adventitia of the ductus was a poorly defined layer of fibrous connective tissue in continuity with that of the aorta. The media was mainly composed of loosely arranged smooth muscle fibres in a connective tissue matrix. Very fine, wavy elastic fibres could be seen in the matrix. An internal elastic membrane separated the media from the intima. Nearly all the patent ductus showed a tendency towards obliteration. The intima was thin and usually one-cell thick whereas the inner portion of the media was much thickened and intercellular vacuoles numerous in most cases.

At the ductal-aortic junction, an abrupt proximal junction was observed with a more gradual junction distally (Fig. 3). The elastic lamellae of the isthmus stopped short at the junction. On the other hand, the ductal tissue attenuated slightly into the media of the descending aorta. Elastic tissue from the ductus continued into the distal aorta in some specimens, but in no specimens was there a 'sling' of ductal tissue encircling the aorta.

Histologically the 16 'normal-looking' aortic arches were similar to the other normal arches as was their relation to the ductus except for one case with ventriculoarterial discordance. This particular case showed a comparatively large extension of ductal tissue into the lateral aortic wall.

(ii) COARCTATION AND/OR TUBULAR HYPOPLASIA

These 12 specimens ranged from 1 day to 10 months old in age. All the specimens had varying degrees and lengths of arch narrowing (Fig. 4). In one specimen the isthmus was imperforate. Only 2 specimens had distinct external strictures of the aortic wall in the region opposite the insertion of the ductus. In 4 specimens, the narrowing was limited to the isthmus, that is between the origin of the left subclavian artery and the ductal insertion. The narrowing extended into the aortic arch in 6 specimens affecting the region between the origin of the right brachiocephalic artery and the ductus. The remaining 2 specimens were associated with aortic atresia and gross aortic stenosis, respectively. All but one case were associated with grossly patent or probe patent ductus.

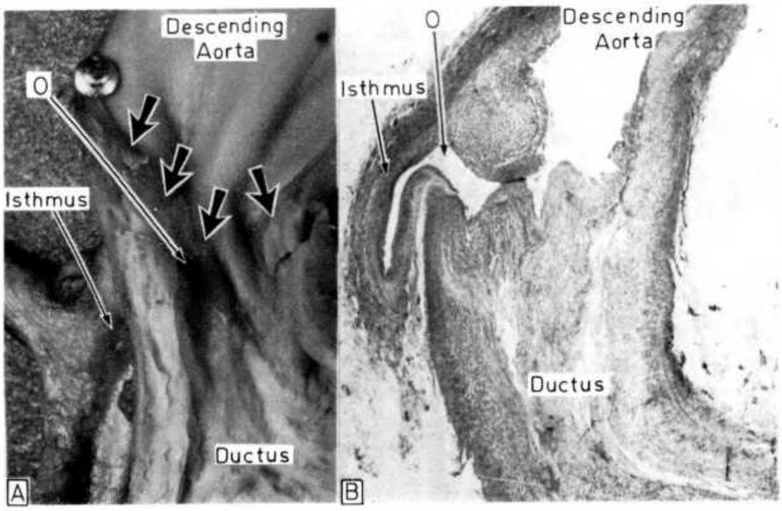


Fig. 5 (A) *Dissection of a specimen with tubular hypoplasia. The isthmus is narrow and its entrance to the ductus —descending aorta junction (O) is surrounded by ductal tissue. The extent of ductal tissue into the descending aorta is marked by the solid arrows.* (B) *Histological section of the same specimen shows the isthmal orifice (O) bound by ductal tissue.* (*Trichrome.* × *13.*)

The morphology of the 12 cases is presented in the Table. All of them were affected by some form of obstruction or restriction to aortic blood flow. Two cases had aortic atresia, and in one of these the arch narrowed from the isthmus towards the heart (Fig. 4, case 3). In the other case the ascending aorta was wider than the isthmus (Fig. 4, case 2).

When the ductus-aorta junction was dissected longitudinally, the coarctation lesion could be seen as a tongue-like structure which suspended mainly from the superoposterior aortic wall and continued as a lesser lesion along the lateral and medial walls. Pulpy ductal tissue was identified in this area in two specimens of tubular hypoplasia. This tissue encircled the orifice of the isthmus (Fig. 5A).

When the junction was examined histologically, pale staining ductal tissue could be traced as a sling along the luminar surface of the aorta in 6 of the cases with tubular hypoplasia. This sling was usually as wide as the ductus and stretched from the ductal insertion along the superior, medial, and inferior walls of the aorta. The ductus were probe patent in all these cases though they all showed evidence towards closure.

In 4 cases with hypoplastic arches but without localised external strictures, the extensions of ductal tissue into the aorta were seen to be obstructive to aortic flow. In 3 cases, ductal tissue produced a raised diaphragmatic-like structure at the entrance of the isthmus to the descending aorta (Fig. 5B). This ridge was thickest on the superior wall of the aorta. On tracing this lesion across the aorta it was definitely found to be in continuity with the ductus at the ductal junction (Fig. 6). In the fourth case the aorta was imperforate at its junction with the ductus. A tongue-like obliterative curtain lesion was responsible for the lack of patency. The tip of the tongue was continuous with the medial ductal wall inferiorly and extended along the lateral sides of the aorta at the ductal junction. The front of the lesion was continuous with the outer ductal media while the back was in continuity with the inner ductal media (Fig. 7).

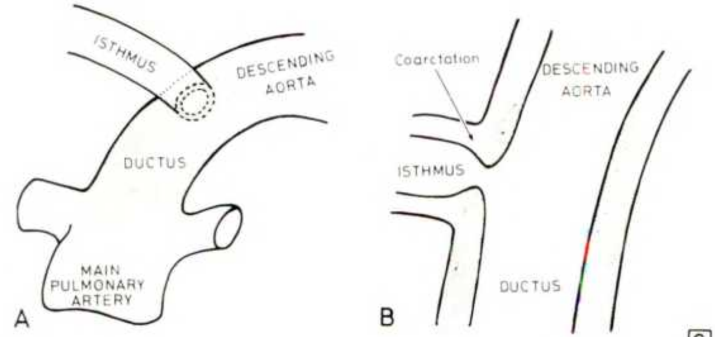


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Fig. 6 (A) *Diagram to show the extension of ductal tissue (stippled) into the descending aorta.* (B) *A longitudinal section to show the diaphragmatic coarctation lesion. Ductal tissue is stippled.*

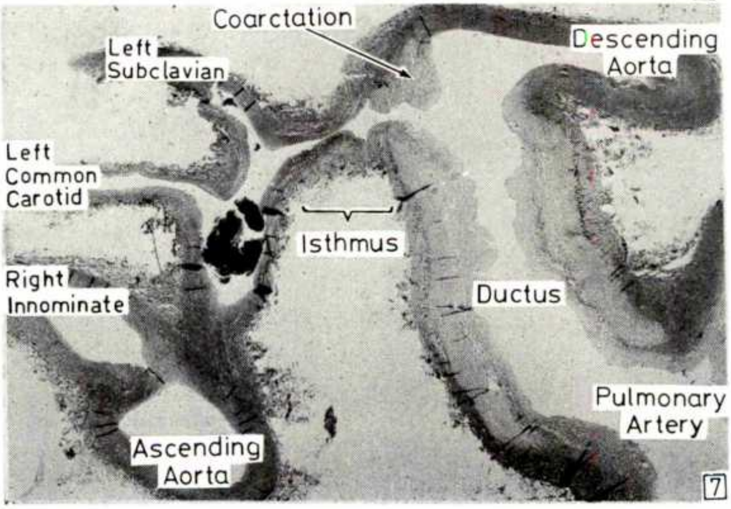

Fig. 7 *Longitudinal section of a specimen from an 8-day-old baby boy which clearly shows that pale staining ductal tissue constitutes the bulk of the coarctation lesion. The isthmus is hypoplastic in this case and there is no evidence of an external localised stricture. (Trichrome. × 8.)*

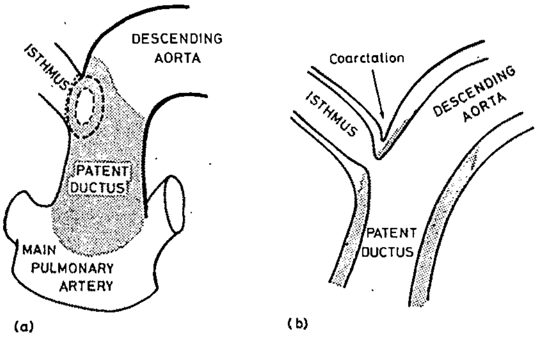

Fig. 8 *Diagram of a specimen with a distinct plication of the aortic wall. Ductal tissue (stippled) still constituted part of the coarctation lesion.*

In the remaining 2 cases the isthmal regions were narrowed in the presence of a curtain-like coarctation lesion. The ductus was closed in 1 case but supplied the descending aorta just distal to the plication of the aorta wall in the other. In each case, pale staining ductal tissue formed the bulk of the coarctation lesion and could be traced to the ductus (Fig. 8).

Discussion

The present investigation lends support to those who have criticised the classical approach of dividing coarctation into 'fetal' and 'adult' types (Calodney and Carson, 1950; Clagett *et al.*, 1954; Sinha *et al.*, 1969; Rudolph *et al.*, 1972; Rosenberg, 1973; Shinebourne and Elseed, 1974). The histological part of the study revealed that half the specimens had a combination of diffuse tubular narrowing and obstructive lesion; none was afflicted by the obstructive lesion alone. Moreover, though the specimens were mainly drawn from a collection of congenitally malformed hearts, the ages of manifestation of symptoms did not correlate with the anatomic types.

It is desirable to consider diffuse tubular narrowing and localised narrowing which occurs in conjunction with an obstructive lesion as separate entities for a more precise evaluation as causes of congestive heart failure (Sinha *et al.*, 1969). It has been proposed that 'coarctation' be used solely to refer to the localised narrowing and its obstructive lesion (Edwards, 1953; Sinha *et al.*, 1969; Shinebourne and Elseed, 1974). Tubular hypoplasia as designated by Edwards (1953) refers to a zone of diffuse narrowing of the aortic arch. However, it does not preclude the occurrence of an obstructive lesion. As Rosenberg (1973) pointed out, histological examination may be needed to identify the obstructive lesion in tubular hypoplasia. Be that as it may, the distinction between coarctation and tubular hypoplasia seems important, and in the subsequent discussion the term 'coarctation' will be restricted to the presence of an obstructive curtain lesion.

In the specimens we have studied coarctation was always associated with tubular hypoplasia though the converse was not always the case. Abbott (1928) observed that the sharply localised constriction usually occurs after some preliminary narrowing and Sinha *et al.* (1969) reported a 78 per cent association of the two arch anomalies. This finding is contrary to Rudolph and co-workers' statement (1972) that coarctation associated with isthmal narrowing is unusual. The external stricture of the aorta recognised as a prerequisite in distinguishing coarctation from tubular hypoplasia by many authors (Edwards *et al.*, 1948; Clagett *et al.*, 1954; Sinha *et al.*, 1969; Rudolph *et al.*, 1972; Rosenberg, 1973; Shinebourne and Elseed, 1974) is not always present even though an obstructive lesion is found anatomically.

Contrary to the beliefs of workers such as Rokitansky (1852) and Hutchins (1971), the normal ductus arteriosus has a different structure from its adjoining great arteries. When incised, the normal obliterating ductus of the human specimen has a pulpy appearance in contrast to the smooth inner wall of the aorta or pulmonary artery. Histologically, the difference is even more striking, as endorsed by many workers such as Langer (1857), Jager and Wollenman (1942), Everett and Johnson (1951), Noback *et al.* (1951).

The obstructive curtain lesion as described by Rudolph *et al.* (1972) is perhaps a misnomer as it is not merely a shelf which protrudes from the left and posterior aspects of the aortic wall immediately opposite the attachment of the ductus. Rather it encircles the aorta more like a diaphragm, originating from the ductal insertion. With regard to this, Claggett *et al.* (1954) and Rudolph *et al.* (1972) opined that ductal tissue was unlikely to have extended into the aortic wall because the curtain lesion was opposite the ductal attachment rather than in contiguity with it. The present findings in no way support this contention. Indeed, the histological study of 6 specimens with the coarctation lesion revealed that ductal tissue made up a substantial part of the lesion, and completely surrounded the aortic lumen. Histological study further confirmed the naked-eye observation of ductal tissue entirely surrounding the isthmal orifice like a diaphragm. This observation supports strongly the findings of Wielenga (1959), Brom (1965), and Rosenberg (1973). The other 6 specimens with only tubular hypoplasia also exhibited a ductal sling around the aorta, albeit that the ductal tissue was mostly restricted to a thin layer lining the lumen.

Hypotheses on the pathogenesis of coarctation in relation to the ductus have mostly designated the ductal tissue in the aorta as 'ectopic', that is as an excessive spread of ductal tissue into the aorta (Craigie, 1841; Skoda, 1855; Bonnet, 1903; Krediet, 1965; Brom, 1965; Wielenga and Dankmeijer, 1968). The results of the present study suggest that the ductal tissue sling found in the aortic wall is not ectopic but rather represents the original distal wall of the sixth left arch as proposed by Rosenberg (1973). The ductus and descending aorta form a common channel of structural continuity and the isthmus enters this channel rather than the converse. Thus, though all the cases studied had evidence of lesions that would have reduced flow through the aorta, and to this extent support flow theories for coarctation (Rudolph *et al.*, 1972), they also paradoxically show that the ductus forms a sling which 'lassoes' the aorta. They therefore additionally support the 'Skodaic' hypothesis, which should not be dismissed as being without foundation (Shinebourne and Elseed, 1974).

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Developmental anatomy of the membranous part of the ventricular septum in the human heart

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SUMMARY The anatomy of the membranous part of the ventricular septum is described in 25 hearts from patients ranging in age from 15 weeks of gestation to the ninth decade of adult life. Both atrioventricular and interventricular components were recognised in all the adult subjects, and the atrioventricular component was evident in all 25. The interventricular membranous septum was present in only 1 of the fetal hearts and 4 of the infant subjects. We consider that these findings indicate that the transformation of the membranous septum into atrioventricular and interventricular components occurs in the late fetal and early postnatal period rather than during closure of the embryonic interventricular foramen. It is associated with the liberation of the medial leaflet of the tricuspid valve from the muscular ventricular septum.

The morphology of the membranous part of the ventricular septum is well described, particularly its division into atrioventricular and interventricular components (Walmsley, 1930; Odgers, 1938). However, can we be sure how these components are produced? Odgers (1938), endorsed by Goor *et al.* (1970), argued that the atrioventricular component resulted from fusion of the right bulbar ridge with the right lateral atrioventricular cushion, while the interventricular component was formed by proliferating tubercles so as to obliterate the embryonic interventricular foramen. While this may be the mechanism of closure of the foramen, it is hard to envisage it producing two components of the membranous septum. This is because the septum is divided into its portions by the annular attachment of the tricuspid valve leaflets, and these leaflets are as yet unformed at the time of closure of the secondary interventricular foramen. This fact has important consequences, because defects of the two components of the membranous septum are explained on the basis of different anomalous growth pattern (Goor and Lillehei, 1975). If the tricuspid leaflets are indeed formed late, this explanation would not be possible because any hole in the position of the membranous septum would be atrioventricular. Presence of an interventricular defect would be dependent upon the secondary formation of the tricuspid annulus and its relation to the membranous septum. In an attempt, therefore, to elucidate the mode of formation of the components of the membranous septum, we have studied its morphology in fetal, infant, and adult human hearts.

Subjects

Twenty-five hearts were studied. Five were from fetuses of 15 to 26 weeks' gestation, 10 were from infants from stillbirth to 1 year of age, and the remaining 10 were from subjects aged from 3 years to 85 years. This latter group was designated 'adult', though 3 hearts were from children aged 3, 5, and 8, respectively. These were considered as juvenile adults for the purpose of this study. None of the subjects had died from heart disease but coronary artery disease was evident in some of the elderly subjects. The fetal hearts were studied by histological sectioning, as were the neonatal hearts. The hearts were embedded in their entirety in paraffin wax and serial sections of 10 μ thickness were prepared. One section in each 25 was mounted and stained with Masson's trichrome technique. The adult hearts were opened to expose both left and right aspects of the membranous septum. The hearts were then photographed from both left and

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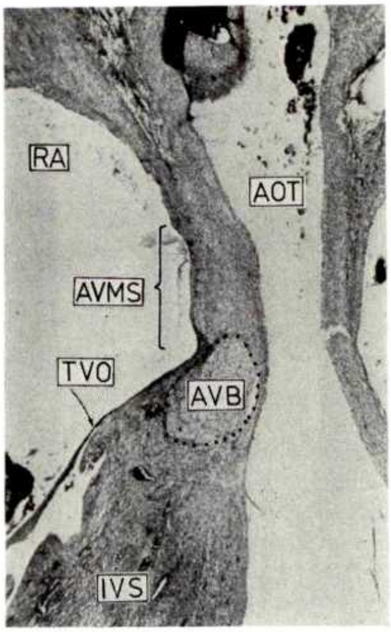


Fig. 1 *Photomicrograph of the region of the membranous septum from a 30-week gestation fetus. The membranous septum is placed solely between the aortic outflow tract (AOT) and the right atrium (RA). It is solely atrioventricular membranous (AVMS), because the origin of the tricuspid valve (TVO) has yet to be liberated from the interventricular septum (IVS). Note the location of the atrioventricular bundle (AVB).*

right sides. The specimens were pinned on a cork board, with the area to be illustrated over a circular hole, 6·5 cm in diameter, cut out of the cork. They were illuminated from behind with one lamp of a Schott KL 150B fibreoptic lamp operated at one-third to one-half of its strength.

Results

(1) FETAL HEARTS

The atrioventricular component of the membranous septum was evident from gross examination in each case. Only 1 of the 5 had an interventricular component which was small, but this structure could not be identified in the remaining 4. Microscopy confirmed these findings (Fig. 1). The anteroseptal commissure of the tricuspid valve was attached directly to the muscular crest of the ventricular septum. The annular attachment of the valve overlaid the penetrating atrioventricular bundle, placing the entire membranous septum in the atrioventricular position.

(2) INFANT HEARTS

The anatomy of the membranous part of the septum varied considerably in the infant hearts (Fig. 2 A, B, C). Two hearts possessed both atrioventricular and interventricular components. In both, the atrioventricular component was large, while the interventricular part, beneath the medial leaflet of the tricuspid valve, was rudimentary. The medial leaflet itself was 'fetal' in appearance, being still

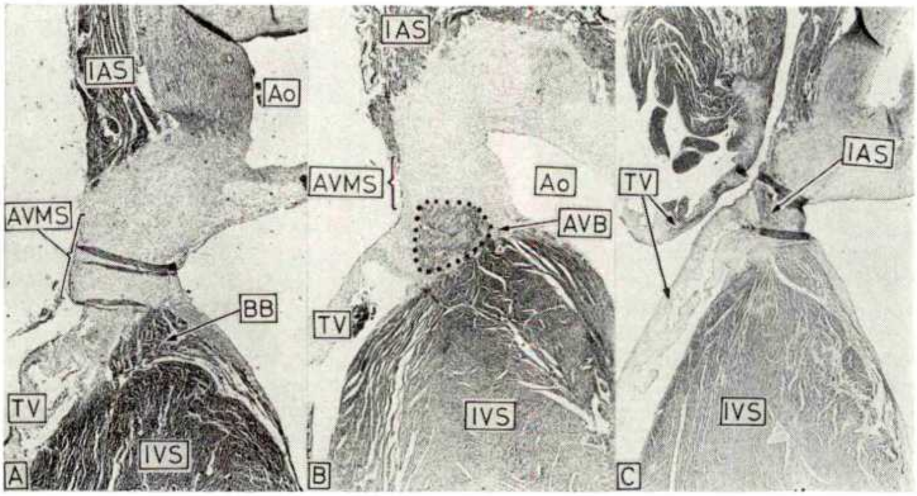


Fig. 2 *A series of sections of the membranous septal area in infant hearts. (A) The origin of the tricuspid valve (TV) placed the membranous septum in an atrioventricular position. (B) The origin is a little higher but still the septum is atrioventricular, the interventricular component being filled by the atrioventricular bundle (AVB). (C) There is virtually no membranous septum because the atrial septum comes almost down to the ventricular septum. IAS, interatrial septum; Ao, aortic outflow tract. Others as before.*

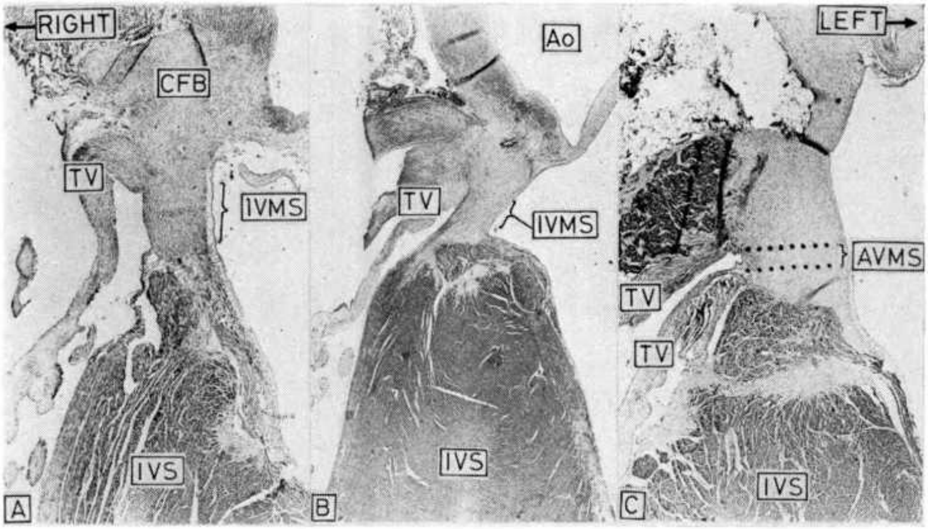


Fig. 3 *Further sections of infant hearts showing the membranous septal origin. All sections are at the entire extent of the membranous septum. (A) and (B) A small interventricular component is illustrated. (C) However, the membranous septum is atrioventricular.*

partially attached to the endocardium of the muscular septum (Fig. 3). In the remaining hearts, the annulus of the tricuspid valve was positioned so as to place the entire membranous septum in an atrioventricular position except in 2 hearts where a membranous septum as such was not identified, the musculature of the right atrium overlying that of the ventricular septum (Fig. 4).

(3) ADULT HEARTS

Both atrioventricular and interventricular components were present in each heart, but because the topography of the membranous part of the septum was slightly different in the juvenile hearts they are described separately from the mature adult specimens.

(*a*) *Young subjects*

When transilluminated, the atrioventricular component appeared as a triangle, with the commissure of the inferior and medial tricuspid leaflets as its base (Fig. 5A). The apex was thinly overlaid with

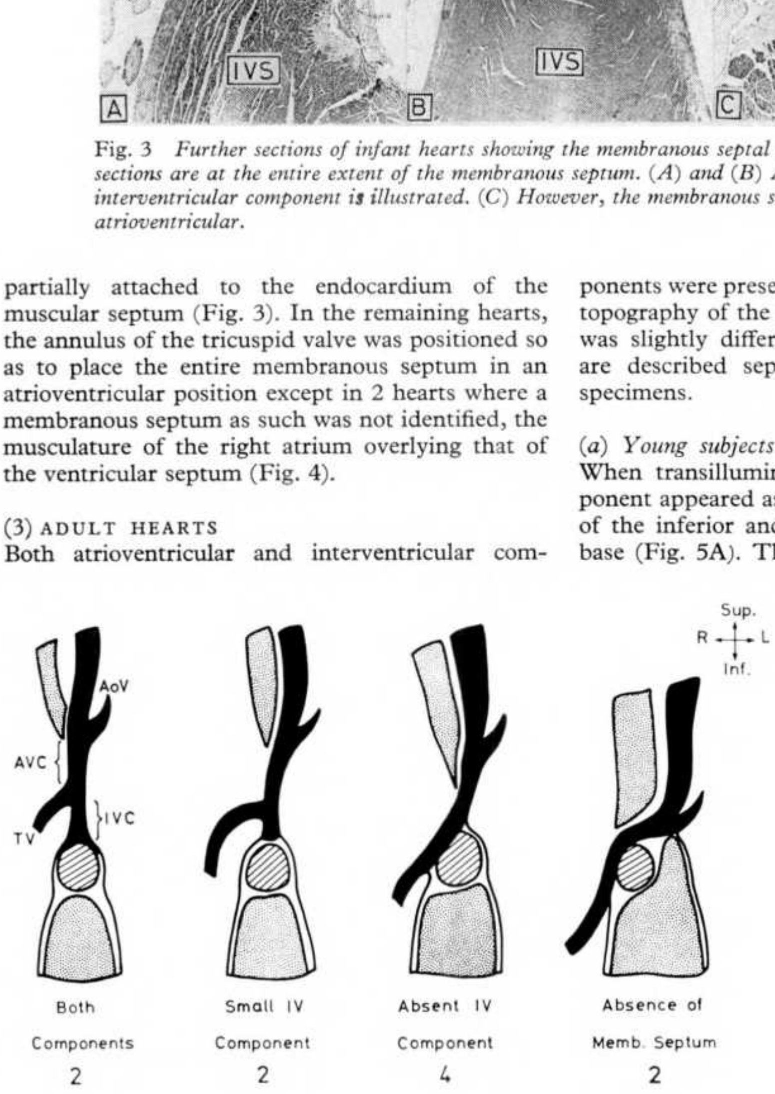


Fig. 4 *Diagram illustrating the components of the membranous septum found in 10 infant hearts studied by serial sectioning. AVC, atrioventricular component; IVC, interventricular component; AoV, aortic valve.*

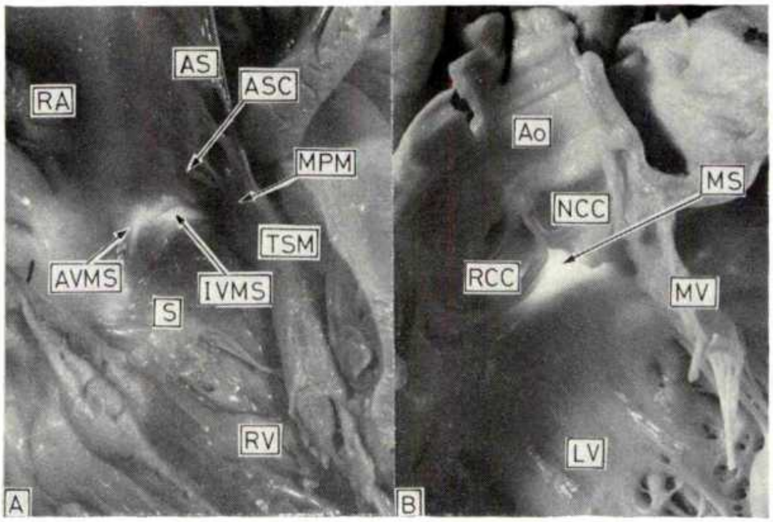


Fig. 5 *Photographs from a child aged 5 years illustrating the components of the membranous septum. (A) A view from the right side with the membranous septum transilluminated from the left. The membranous septum has both atrioventricular (AVMS) and interventricular (IVMS) components, the two separated by the insertion of the tricuspid valve. S, septal leaflet; AS, anterosuperior leaflet of tricuspid valve; ASC, anteroseptal commissure; MPM, medial papillary muscle; TSM, trabecula septomarginalis; RA, right atrium; RV, right ventricle. (B) the left ventricular aspect transilluminated from the right. The membranous septum (MS) is beneath the right (RCC) and non (NCC) coronary cusps of the aorta (Ao). LV, left ventricle; MV, mitral valve.*

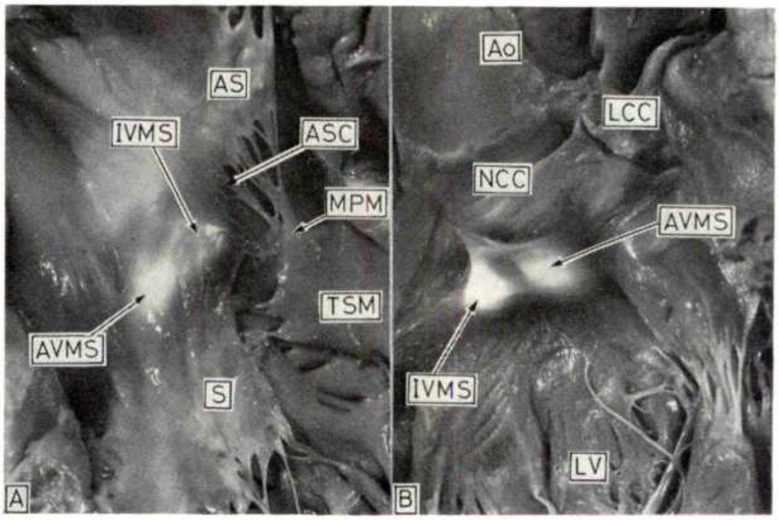


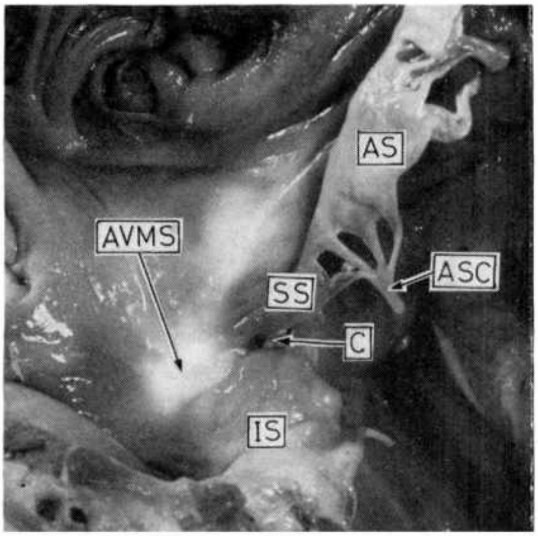
Fig. 6 *(A) and (B) Photographs of the membranous septum region in a 45-year-old man. By this age both components are well formed. The specimen has been transilluminated as for Fig. 5. The shadow is that of a wire passed beneath the medial tricuspid leaflet to differentiate the atrioventricular and interventricular components of the membranous septum.*

atrial muscle fibres. The atrioventricular portion of the membranous septum measured 9 to 10 mm. The interventricular component of the membranous part of the septum occupied the area beneath the commissure of the inferior and septal leaflets of the tricuspid valve. It extended anteriorly and inferiorly to the medial papillary muscle. All 3 child hearts had secondary chordae tendineae attaching the ventricular surface of the medial tricuspid leaflet to the interventricular membranous septum.

When seen from the left ventricle, the membranous part of the septum appeared between the middle of the right aortic cusp and the posterior (non-coronary) aortic cusp (Fig. 5B). The septum was again triangular in shape, ranging in size from 7 × 5 mm in the 3-year-old to 11 × 7 mm in the 8-year-old.

(*b*) *Mature subjects*

In younger adults the atrioventricular septum was not well seen without transillumination, but was a conspicuous feature in subjects over 45 years old (Fig. 6A and B). In one of the oldest hearts, a fairly large artery traversed the atrioventricular membranous septum. Measurements of the atrioventricular septum indicated that it varied considerably in size from 7 × 3 mm to 18 × 12 mm.



The interventricular membranous septum lay beneath the tricuspid valve as in the juvenile hearts, but was in less intimate relation to the medial papillary muscle, especially in those over 60 years of age. In the 2 oldest subjects (80 plus), the septal leaflet was elaborately scalloped, producing a distinct cleft between its superior and inferior components (Fig. 7). The interventricular membranous septum was usually triangular or, in younger adults, pear-shaped, and varied in size from 4 × 5 mm to 10 × 10 mm.

When viewed from the left ventricle, the membranous septum was variable in size and measured from 10 × 5 mm to 16 × 8 mm. It lay between the middle of the right aortic cusp to the middle of the posterior cusp, as in the children's hearts. However, in some adults, irrespective of age, the membranous part of the septum originated posterior (to the left) of the right aortic cusp, and extended postero-inferiorly to the base of the anterior commissure of the mitral valve. The atrioventricular component of the septum was consistently larger than the interventricular component.

Discussion

Our findings show unequivocally that in the majority of fetal and infant hearts the membranous septum has only an atrioventricular component. The conversion of this infant arrangement to the pattern described by Walmsley (1930), and more usually illustrated in textbooks of anatomy (Walmsley in *Quain*, 1929; Gray, 1973), is dependent upon undermining of the tricuspid valve leaflets in the region of the septum. This process results in the annular attachment of the valve extending from the crest of the muscular septum to a position where it crosses the membranous septum, converting it into its typical atrioventricular and interventricular components (Fig. 6B). The evidence of this undermining is to be found in the constant presence of chordae tendineae attaching the ventricular aspect of the foramen, though this is also a contentious point. It is not always appreciated that the foramen which is closed to bar the aorta from the right ventricle is the secondary interventricular foramen, the primary foramen becoming the aditus to the aortic outflow tract (Frazer, 1931; Van Mierop *et al.*, 1963). Neither is this precise origin of the tissue which finally closes the secondary foramen agreed upon (Odgers, 1938; Wenink, 1974). However, the nature of closure of the foramen is clearly a separate process from undermining of the tricuspid valve leaflets, since at the time of closure, which all agree to be at about Horizon XVIII (that is about 6 weeks of gestation), there is no evidence of formation of the septal leaflet of the tricuspid valve. Until the septal leaflet is formed and undermined relative to the membranous septum, there can be no justification for referring to atrioventricular and interventricular components of the septum.

This point has major significance with regard to the nomenclature of defects of the ventricular septum. Defects in the region of the ventricular component of the membranous septum are commonly referred to as 'membranous' defects. Warden and his colleagues (1957) previously indicated quite rightly that most so-called 'membranous' defects were considerably larger than the area of interventricular membranous septum observed in the human heart. Our findings of absence of this component in the majority of fetal and infant hearts give added weight to their contention that 'membranous' is an inappropriate term for such defects. Our morphological studies (unpublished observations) suggest that defects result either from a deficiency of the muscular septum adjacent to the membranous component, or else to malalignment of the aorta with the left ventricle. For these reasons we suggest that 'perimembranous septal defect' would be a more appropriate name for defects confluent with the pars membranacea septi. Our findings are also pertinent to the morphology of defects which exist between the left ventricular outflow tract and the right atrium. These defects are frequently explained on the basis of absence of the atrioventricular component of the membranous septum (Goor and Lillehei, 1975). This should not be taken to indicate that the interventricular component of the septum is normally formed and intact. In a current study of over 200 hearts with isolated ventricular septal defects (Soto, B., Becker, A. E., Moulaert, A., Lie, J. T., and Anderson, R. H., unpublished observations), the only hearts we observed with right atrial to left ventricular communications possessed typical perimembranous defects but associated with a wide anteroseptal commissure of the tricuspid valve. The absence of a tricuspid attachment in the region of the commissure placed the defect in direct communication with the right atrium, a possibility envisaged by Rosenquist and Sweeney (1975) following study of normal hearts, and also described by Warden *et al.* (1957). The question is therefore raised as to whether the right atrial—left ventricular communication warrants a separate category when considering the nosology of septal defects. Only further surgical-anatomical studies will clarify this point.

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Morphological variations in pulmonary atresia with intact ventricular septum

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SUMMARY The morphological features of a series of 37 specimens of pulmonary atresia with intact ventricular septum were reviewed with particular emphasis on features which might influence the results of pulmonary valvotomy. The degree of right heart hypoplasia was quantified by measuring right and left heart dimensions and comparing them with 20 normal infant hearts. Right ventricular cavity size was usually smaller than normal but constituted a spectrum ranging from tiny to a dilated ventricle larger than normal. There was a positive correlation between triscuspid annular size and right ventricular size but no correlation between the size of the pulmonary artery and the right ventricle. Successful pulmonary valvotomy with subsequent adequate right ventricular function would have been precluded by a tiny right ventricular cavity or infundibular atresia in 14 specimens and by severe tricuspid stenosis or regurgitation in an additional 4. Severe right or left ventricular endocardial fibroelastosis may have adversely affected ventricular function in several others. Ten specimens displayed convex bulging of the left ventricular septal surface. If these anatomical findings are representative for the condition as a whole, they provide a good explanation for its disastrous prognosis.

The life of an infant born with pulmonary atresia and an intact ventricular septum is likely to be brief and stormy. Medical treatment is unavailing and survival depends upon the surgical establishment of a reliable source of pulmonary blood flow, either by a systemic-pulmonary artery shunt, by pulmonary valvotomy, or by both. Whatever techniques are employed, surgical mortality remains disappointingly high (Trusler *et al.*, 1976). It is possible that the right heart hypoplasia known to be common with pulmonary atresia could account for these disappointing results. However, there is no agreement concerning the nature and frequency of this hypoplasia. Greenwold *et al.* (1956) believed that right ventricular cavity size could be classified as small or large and this view was endorsed by Davignon *et al.* (1961) and Celermajer *et al.* (1968). In contrast, others have contended that cavity size constitutes a spectrum (Gersony *et al.*, 1967; Bowman *et al.*, 1971; Murphy *et al.*, 1971). As cardiac morphology must influence surgical results, particularly if an effort is made to establish a communication between right ventricle and pulmonary artery, we have undertaken a review of the morphological features of pulmonary atresia, including measurements of right and left heart dimensions and their comparison with those of a series of normal infant hearts.

Subjects and methods

Thirty-seven infant hearts with pulmonary atresia and intact ventricular septum together with 3 hearts with critical pulmonary stenosis were found in the cardiopathological collections of the Brompton Hospital, Cardiothoracic Institute (London); Killingbeck Hospital (Leeds); Institute of Child Health, Alder Hey Hospital (Liverpool); and Grimsby General Hospital (South Humberside). These specimens were examined and compared with 20 normal infants' hearts from the Wilhelmina Gasthuis (Amsterdam). Emphasis was on those particular features which might have a bearing on selection of the optimal surgical approach and on its outcome; specifically, the size and morphological

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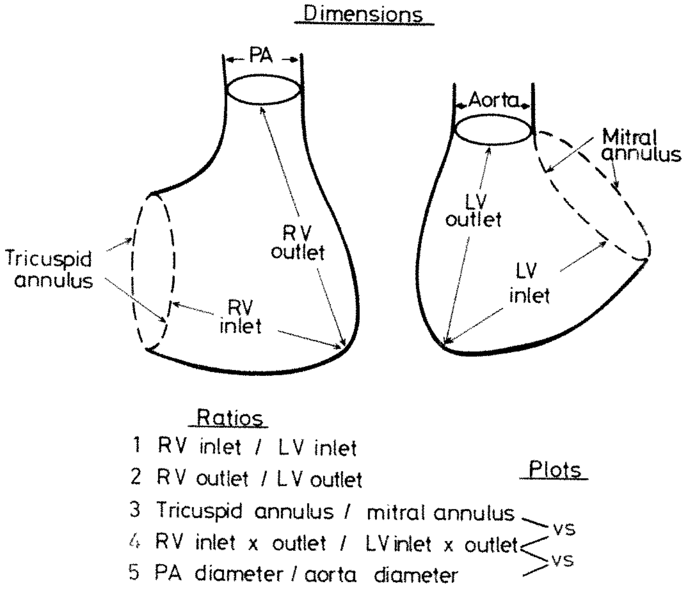

Fig. 1 *Diagram showing measurements, ratios, and plots obtained. RV, right ventricle; LV, left ventricle; PA, pulmonary artery; vs, versus.*

features of the tricuspid and pulmonary valves, the right ventricular cavity, and the pulmonary artery. The inlet and outlet dimensions of the right and left ventricles, the circumference of the tricuspid and mitral annuli, and the diameters of the pulmonary artery and aorta were measured (Fig. 1). Ratios between each right-sided measurement and its corresponding left-sided dimension were calculated as was the ratio of the product of the inlet and outlet dimensions of the right and left ventricles. The ratio of the products of right to left ventricular inlet and outlet measurements was plotted against both the tricuspid to mitral annulus ratio and the pulmonary to aortic diameter ratio.

Abnormalities of the tricuspid valve which might have influenced function, such as Ebstein's anomaly, leaflet dysplasia, or abnormal chordal or papillary muscle attachments were searched for and the likelihood of either regurgitation or of stenosis out of proportion to the annular or right ventricular size was noted.

In each specimen the right ventricular cavity size was subjectively graded as tiny, small, normal, or dilated. The cavity was judged to be tiny if deemed too small to sustain life were right ventricular to pulmonary artery continuity to be established. The categories small, normal, and dilated are self-explanatory. The presence of infundibular stenosis or atresia was noted. The presence of endocardial fibroelastosis, grossly visible myocardial sinusoids, and the degree of trabeculation of the

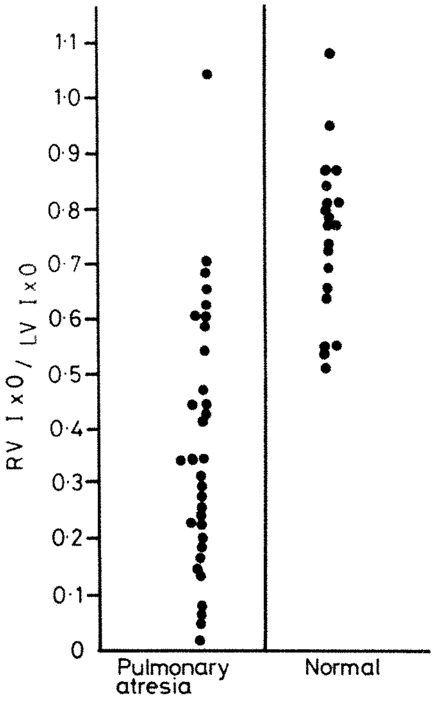

Fig. 2 *Comparison of relative right ventricular cavity size in normal hearts with pulmonary atresia and intact ventricular septum. RVI × 0, product of right ventricular inlet and outlet dimensions; LVI × 0, product of left ventricular inlet and outlet dimensions. Measurements were possible in only 33 specimens.*

right ventricle were recorded. The myocardial thickness in the inlet, outlet, and apical portions of each ventricle was measured.

The morphological characteristics of the pulmonary valve itself were noted, including the number of cusps, extension of commissural ridges to the centre of the valve, and, in the case of critical pulmonary stenosis, the size of the pulmonary valve orifice. The length, outer diameter, and patency of the ductus arteriosus were noted, as was the presence or absence of left ventricular septal bulging.

Results

There was considerable variability in right ventricular cavity size in the group of normal hearts and an even greater range in specimens with pulmonary atresia. In general, the right ventricular cavity was smaller than normal with pulmonary atresia, but there was overlap between pulmonary atresia and normal as indicated by the ratios of the product of the inlet and outlet dimensions in right and left ventricles (Fig. 2). In all 12 cases judged to have a tiny right ventricle the infundibulum was either atretic or stenosed, atresia being present in 8 of the hearts. Infundibular atresia was also observed in 1 heart with a small right ventricle but in none of the hearts judged to have normal or large right ventricular cavity size. Infundibular stenosis, however, was found in 8 of 13 cases judged to have small right ventricles together with 1 heart with a normal-sized right ventricle and 1 heart with a large right ventricle. The right ventricle was of normal size in 2 specimens with critical pulmonary stenosis and large in the third. Grossly evident right ventricular endocardial fibroelastosis was found in 10 cases. There was little correlation with heart size, fibroelastosis being found in small and normal sized right ventricles as well as in tiny ones.

Right ventricular trabeculations were shallow and inconspicuous in most specimens, and myocardial sinusoids were grossly visible in several. In 20 hearts it was not possible accurately to measure myocardial thickness of both right and left ventricles in their apical and outlet portions, but this was possible in most specimens in the inlet portion. In two-thirds of the specimens with pulmonary atresia the right ventricular inlet wall was as thick or thicker than the left ventricular inlet wall.

In 11 specimens the pulmonary valve had been destroyed or greatly altered by surgery, and in 3 cases with a tiny main pulmonary artery no pulmonary valve leaflets were visible. In the remaining specimens 2 types of atretic pulmonary valve were seen. In the first type, prominent commissural ridges converged and met at the centre of the 'valve' (Fig. 3a). This type of pulmonary 'valve' was invariably associated either with infundibular atresia or with a severely stenotic or regurgitant tricuspid valve. The second type of pulmonary valve had commissural ridges present only at the periphery of the membranous pulmonary valve, the centre being smooth and bulging into the pulmonary trunk (Fig. 3b). In 1 specimen the pulmonary valve was bicuspid and in 1 quadricuspid. In each of the 3 cases with critical pulmonary stenosis, the pulmonary valve was thin and dome-

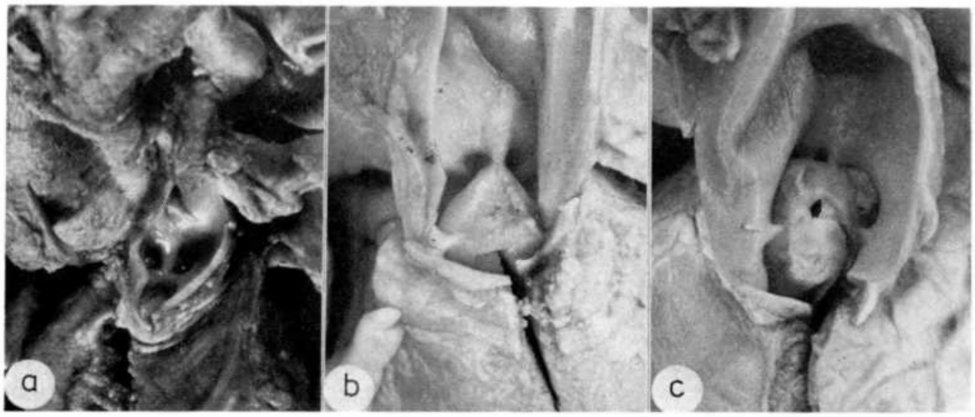

Fig. 3 *The pulmonary 'valve'. (a) Commissural ridges extending to the centre of the 'valve'. (b) Commissural ridges at the periphery of the valve. The centre is smooth and convex towards the pulmonary trunk. (c) Critical pulmonary stenosis with a tiny central orifice. Measurements were possible in only 36 specimens.*

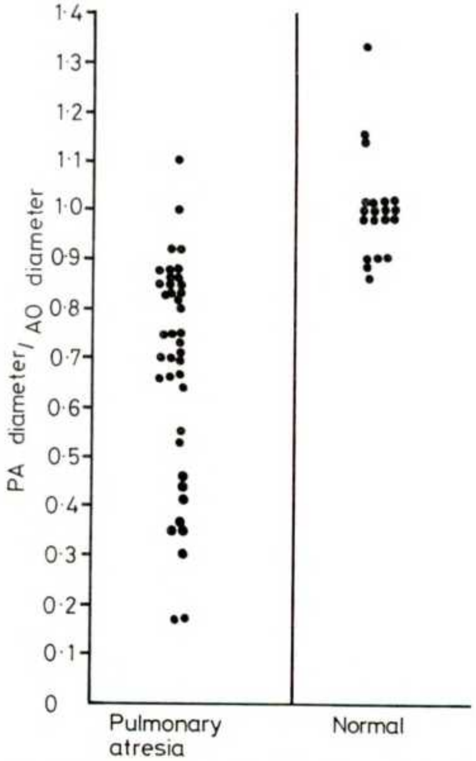

Fig. 4 *Comparison of relative pulmonary artery size in normal hearts and in specimens with pulmonary atresia and pulmonary stenosis and with intact ventricular septum. AO, aorta; PA, pulmonary artery.*

shaped with a central orifice less than 1 mm in diameter (Fig. 3c).

The size of the pulmonary artery, as judged from the ratio of pulmonary artery to aortic diameter, is shown in Fig. 4. Though the pulmonary artery size was small in a few specimens, the overlap with normal was large. The size of the pulmonary artery did not correlate with right ventricular cavity size, a tiny right ventricular cavity often supporting a normal-sized pulmonary artery (Fig. 5). In only 3 cases was the main pulmonary artery strikingly small and in each the right ventricle was tiny.

The size of the tricuspid annulus, as judged by the ratio of the circumference of the tricuspid annulus to that of the mitral annulus, is shown in Fig. 6. In most specimens the tricuspid annulus was smaller than normal. There was a positive correlation between the size of the tricuspid annulus and that of the right ventricular cavity (R = 0·84). Tricuspid valve abnormalities found in this series are shown in the Table. The tricuspid leaflets (including those of patients with critical pulmonary stenosis) varied between normal (Fig. 7a), moderate dysplasia (Fig. 7b), and severe dysplasia (Fig. 7c). There was little correlation between the degree of dysplasia and the size of the tricuspid annulus or of the right ventricular cavity, very dysplastic leaflets being found in some specimens with normal-sized right ventricular cavity and normal tricuspid annular circumference and nearly normal leaflets sometimes being associated with a tiny right ventricular cavity.

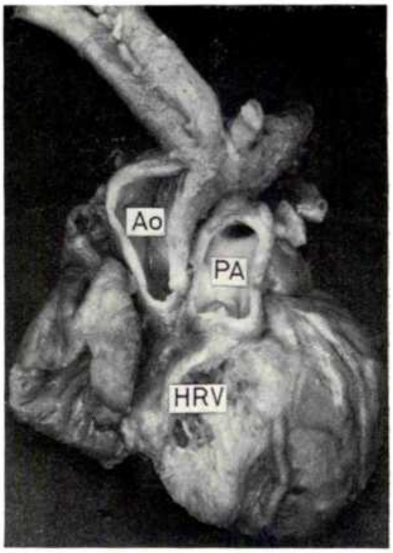

Fig. 5 *A normal-sized pulmonary artery (PA) arising from a very small right ventricle (HRV).*

Ebstein's anomaly, defined as displacement of the effective atrioventricular orifice into the right ventricle, was present in 10 specimens. In 6, the contiguous parts of the septal and inferior leaflets originated at a distance from the tricuspid annulus, the anterior leaflet arising normally (Fig. 8a). In 4 specimens, the tricuspid leaflets were replaced by a fibromuscular membrane extending from the anterior tricuspid annulus to the junction of the inlet with the outlet and trabecular portions of the right ventricle (Fig. 8b, c). In each of these the 'tricuspid' orifice consisted of a single small restrictive perforation in the membrane and was thus displaced far into the right ventricular cavity.

Tricuspid stenosis out of proportion to the right ventricular size was present in 7 cases. The obstruction was caused by heaped up dysplastic septal leaflet tissue in 2 cases of Ebstein's anomaly and appeared to be mild. In the cases of Ebstein's anomaly with a perforate membrane the 'tricuspid' obstruction was severe. In a sixth

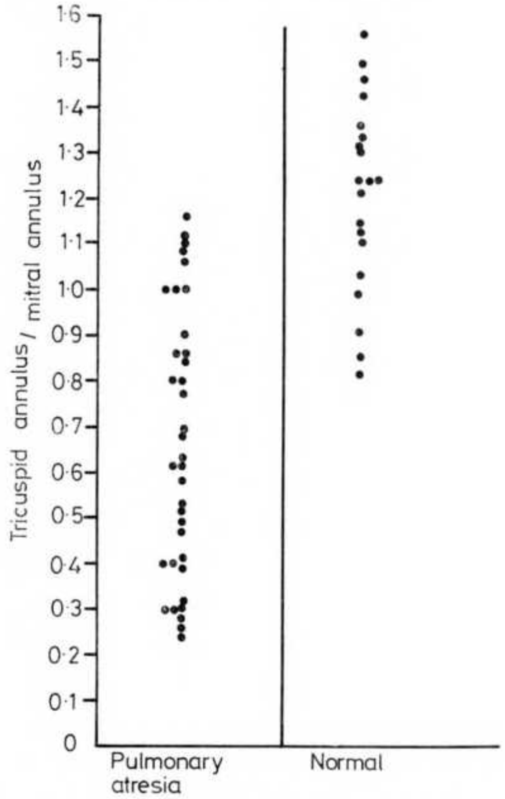

Fig. 6 *Comparison of the relative tricuspid annular size in normals and in specimens with pulmonary atresia and intact ventricular septum.*

Table *Incidence of Ebstein's anomaly and of varying degrees of dysplasia of the tricuspid leaflets in pulmonary atresia.*

	RV cavity				
	Tiny	*Small*	*Normal*	*Large*	*Total*
Ebstein's	5	3		2	10
Tricuspid leaflets					
Very dysplastic	3		1		4
Moderately thick		5	2		7
Slightly thick	2	4	5		11
Normal	2	1	1	1	5

specimen with severe tricuspid stenosis, both anterior and septal leaflets attached directly to a single anterior papillary muscle, constituting a 'parachute' tricuspid valve. In the final case the tricuspid valve was 'unicuspid', the sole commissure being an inferior one.

In 4 cases the tricuspid valve gave every impression of having been regurgitant during life. The right ventricle was large in 3 of these and normal-sized in 1. In 2 of the 4, regurgitation was related to Ebstein's anomaly. In the third case the tricuspid leaflets were somewhat thickened but were well formed; there was slight dilatation of the tricuspid annulus and severe dilatation of the right atrium. In the fourth specimen the tricuspid annulus was hugely dilated and the right ventricle large and very thin-walled.

In 11 of the specimens there was convex bulging of the left ventricular septal surface. Whether

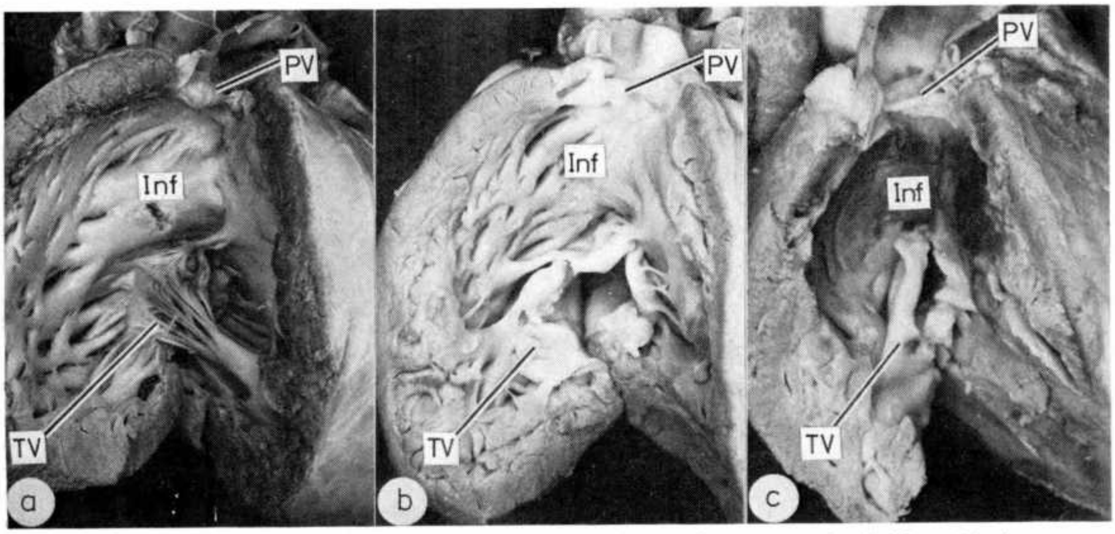

Fig. 7 *Tricuspid leaflets in hearts with critical pulmonary stenosis and pulmonary atresia. (a) Normal (pulmonary stenosis). (b) Moderately dysplastic (pulmonary stenosis). (c) Very dysplastic (pulmonary atresia).*

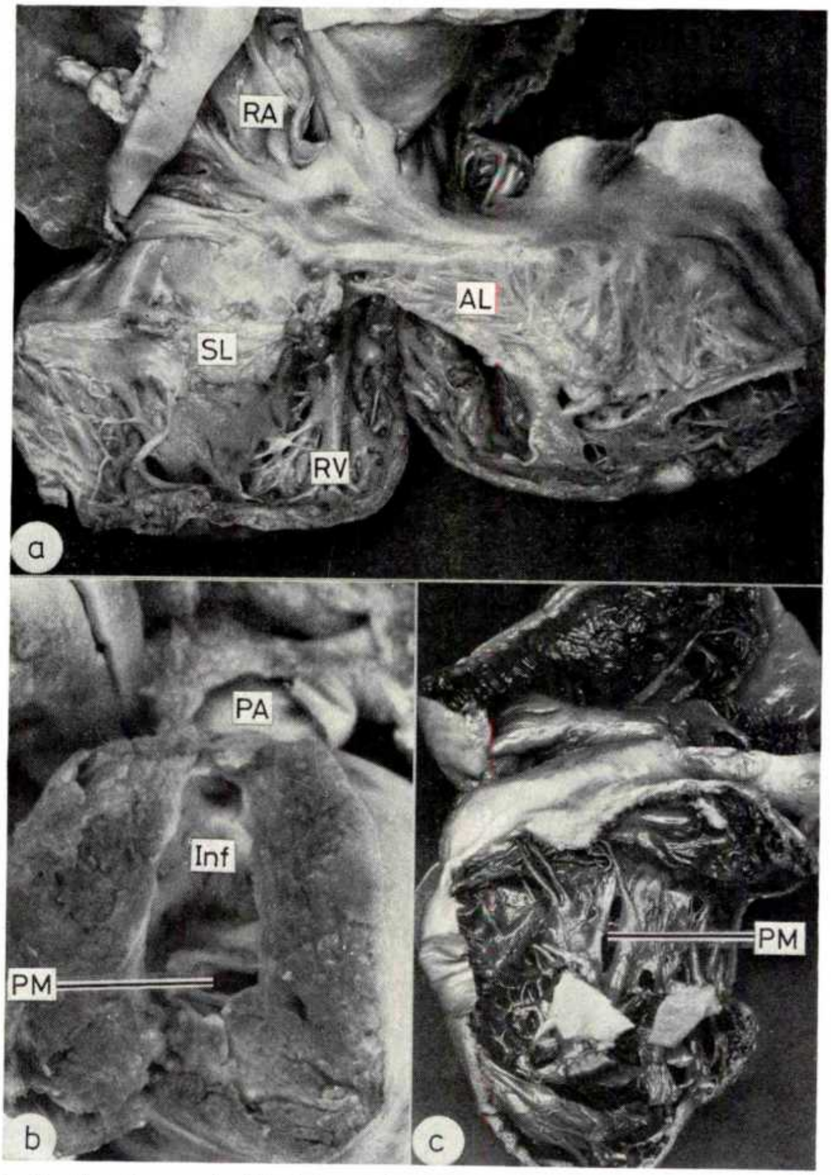

Fig. 8 *Ebstein's anomaly. (a) A view of the right ventricle showing a large anterior tricuspid leaflet (AL) and a displaced septal leaflet (SL). The right ventricle is moderately dilated and thin-walled. (b) A perforate membrane (PM) viewed from the right ventricular outlet portion (Inf.). (c) The anterior wall of the right ventricle has been removed to display a muscularised perforate membrane (PM).*

this could have resulted in subaortic obstruction in any case is conjectural. No discrete subaortic stenosis was seen. Both left ventricular fibroelastosis and an apical aneurysm were present in a single case. The left anterior descending coronary artery was large in 11 specimens, and the posterior descending in 2. The mitral and aortic valves were normal in all specimens. The ductus arteriosus was patent in all unoperated cases and was commonly long and tortuous.

Discussion

Previous observers have disagreed concerning the precise nature of right ventricular hypoplasia in pulmonary atresia with intact septum. Some have argued that cavity size can simply be divided into 'small' and 'large' (Greenwold *et al.*, 1956). Others contend that a spectrum of cavity size is seen (Gersony *et al.*, 1967; Bowman *et al.*, 1971; Murphy *et al.*, 1971). We have tried to obtain objective estimation of this feature by measuring ventricular cavity size and comparing it with similar measurements in the normal heart, as more recently have Freedom *et al.* (1978). Since the size of each measured right heart structure relative to that particular heart seemed more likely to be meaningful than the absolute dimensions themselves, each right heart measurement was related to its left heart counterpart. Each heart, in effect, therefore served as its own control. Such comparisons also lessened the possible artefactual effect of fixation since right and left heart structures should have been equally affected. The results showed that while the specimens were subjectively divided into groups with tiny, small, normal, and dilated right ventricular cavities, the measurements indicated a spectrum of cavity size which overlapped the normal values. These results are in accord with those of Freedom *et al.* (1978).

The size of the right ventricular cavity is the most obvious limiting factor in immediate survival after valvotomy. In the 12 cases with a tiny right ventricle the cavity size alone would have precluded survival after valvotomy done as the sole surgical procedure, the accompanying infundibular atresia or stenosis compounding the situation. Though there have been isolated reports of right ventricular growth after valvotomy (Moller *et al.*, 1970; Bowman *et al.*, 1971; Murphy *et al.*, 1971; Luckstead *et al.*, 1972), there is currently no way of predicting growth potential. The extreme hypoplasia of these tiny right ventricles, the difficulty of outflow tract reconstruction in a newborn infant, and the probable extremely limited potential for growth and function are strong arguments against such a procedure in this group.

Although valvotomy might have been feasible in patients in the small right ventricle group (save the one specimen with infundibular atresia), the degree of infundibular stenosis common to these patients would have necessitated infundibular resection and/or patching, either as a primary procedure (Rigby *et al.*, 1977) or at subsequent surgery (Bowman *et al.*, 1971). In this group the potential for right ventricular growth may be better, but unless the usually associated small tricuspid annulus were to grow as well, tricuspid stenosis would remain (Trusler *et al.*, 1976), and would probably presage a poor prognosis. The cases with dilated right ventricles were also poor candidates for reconstruction; therefore only the cases with near to normal ventricular size could be considered as having a good morphological prognosis.

In the group as a whole the tricuspid valve was the second most common factor limiting the feasibility of success of pulmonary valvotomy. In 5 cases there was a degree of tricuspid stenosis which would have severely limited ventricular inflow, even if a good outflow could have been established. In at least 2 other cases there seemed to have been such severe tricuspid regurgitation that even complete relief of the right ventricular outlet obstruction might not have resulted in a right ventricular outflow sufficient to sustain life. It did not seem likely that either severe tricuspid stenosis or tricuspid regurgitation could have been effectively treated surgically, since relief of inlet obstruction in cases with severe tricuspid stenosis seemed impossible short of resecting the tricuspid valve (or the perforate membrane in the cases with Ebstein's anomaly). A further compounding factor must surely have been the state of the ventricular myocardium. Though an adequate right ventricular cavity and infundibulum, a functional tricuspid valve, and a sizeable pulmonary artery satisfy the plumbing requirements of a successful valvotomy, an effective pump is also required. The right ventricular endocardial fibroelastosis found in 25 per cent of the specimens in our series may have deleteriously influenced myocardial function.

In contrast, the size of the main pulmonary artery was not a limiting factor, only 3 cases being judged too small to have accepted an effective right ventricular output. In all 3, the right ventricular cavity was additionally tiny.

In summary, our anatomical study has shown a range of morphological features in pulmonary atresia with intact septum which shows that surgical treatment must be tailored to each individual case. Thus, pulmonary valvotomy did not seem a feasible procedure in half of the cases in this series. Such cases may benefit from an aortopulmonary anastomosis since in the majority of hearts the pulmonary arteries were found to be of good size. Subsequent repair may be possible by constructing a right atrial to pulmonary artery conduit. Only the cases with a near to normal sized right ventricular cavity seemed anatomically suited to complete repair. Similar cases should probably be treated by pulmonary valvotomy as an initial procedure. Our measurements show that the size of the tricuspid annulus bears a positive correlation with cavity size, and this may be a factor of clinical value.

We are grateful to our clinical colleagues who permitted us to study patients previously in their care, namely, Drs. M. C. Joseph, E. A. Shinebourne, J. L. Wilkinson, and O. Scott. Drs. L. M. Gerlis and J. A. Partridge drew our attention to some of the cases studied, and Dr. A. E. Becker made it possible for us to examine the normal hearts. The investigation was supported by a grant from the British Heart Foundation.

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Conduction disturbances after surgical correction of ventricular septal defect by the atrial approach[1]

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SUMMARY Conduction disturbances have been documented after correction of ventricular septal defects by the ventricular route. Recently, repair of the ventricular septal defect has been through the right atrium to overcome damage to the conduction system and a right ventriculotomy.

Thirty-nine children with ventricular septal defects under the age of 5 years were operated upon by the atrial route (group 1). The incidence of conduction disturbances in this group was compared with that occurring in 19 children of comparable age with a ventricular septal defect repaired via a right ventriculotomy (group 2).

Complete right bundle-branch block developed in 13 of 39 children (33·3%) in group 1, compared with 15 of 19 children (78·9%) in group 2. This was a statistically significant reduction in complete right bundle-branch block in group 1. The incidence of left axis deviation occurring with complete right bundle-branch block was similarly statistically reduced. Transient complete heart block and arrhythmias were not statistically different in the two groups.

The atrial approach to the repair of the ventricular septal defect significantly reduced the incidence of complete right bundle-branch block alone and occurring with left axis deviation.

Conduction disturbances after surgical correction of ventricular septal defects have been well documented (Titus *et al.*, 1963; Kulbertus *et al.*, 1969; Downing *et al.*, 1972; Wolff *et al.*, 1970; Godman *et al.*, 1974; Okoroma *et al.*, 1975; Subramanian, 1976; Sigmann *et al.*, 1977). Surgical technique has been implicated. With the introduction of a new approach for the repair of ventricular septal defect via the right atrium, it was hoped to alleviate the problems caused by damage to conduction pathways. Subramanian (1976) noted that there was an incidence of postoperative complete right bundle-branch block in 44·4 per cent of patients who underwent surgery by the transatrial approach. Okoroma *et al.* (1975) found an incidence of 44 per cent in a similar group.

We undertook a retrospective study of 39 children who had transatrial ventricular septal defect repair and compared them with 19 children matched for age and sex who had a ventricular septal defect repaired via a ventriculotomy.

Patients and methods

The present series consists of 58 children with ventricular septal defects confirmed by cardiac catheterisation. They had the surgical repair at The Hospital for Sick Children, Toronto, between January 1973 and December 1976. Their ages were less than 5 years at the time of surgery.

The ventricular septal defect was an isolated lesion in 34 children. In the other 24 children associated lesions were atrial septal defect in 11 patients; persistent ductus arteriosus in 6 patients; persistent ductus arteriosus and atrial septal defect in 1 patient; persistent ductus arteriosus and coarctation of the aorta in 1 patient; infundibular pulmonary stenosis in 4 patients; and atrial septal defect and pulmonary stenosis in 1 patient.

Group 1 patients had the ventricular septal defect

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repaired through the tricuspid valve after right atriotomy. There were 39 children (20 girls; 19 boys) whose ages ranged from 2 months to 4 years and 10 months. Forty-eight patients were submitted for operation but 9 were excluded. Eight children died in the operative period and immediate postoperative electrocardiograms were not available, and 1 child was excluded because of preoperative left axis deviation on the electrocardiogram.

Group 2 patients had the ventricular septal defect repaired after a right ventriculotomy. There were 19 patients (9 girls; 10 boys) whose ages ranged from 8 months to 5 years. Twenty-three patients were submitted for operation but 2 children died in the operative period and were excluded as there were no immedate postoperative electrocardiograms and 2 children were excluded because of left axis deviation on the preoperative electrocardiogram.

In both groups, the majority of ventricular septal defects were of the membraneous variety, 85 per cent in group 1; 89·5 per cent in group 2. All the ventricular septal defects were closed with a patch in group 1 and 84 per cent with a patch in group 2.

The clinical records and operative records were reviewed. The maximum follow-up period was 3 years. All serial preoperative and postoperative electrocardiograms available were analysed for mean QRS axis, QRS duration, PR interval, atrial and ventricular hypertrophy, and arrhythmias. The criteria for left axis deviation were considered to be present if the mean QRS axis was lying between 240° to 360° which is to the left of the accepted normal for children (Moss and Emmanouilides, 1973). Complete right bundle-branch block was present when the duration of the QRS interval was 0·10 s or longer (Guntheroth, 1965). We excluded any child who had electrocardiographic criteria for left axis deviation before surgery and all fatal cases as there were no postoperative electrocardiograms available.

Results

GROUP 1

Of 48 children in group 1, 8 died (16·6%) and of 23 children in group 2, 3 died (13·0%), thus overall mortality in the 2 groups was not statistically different. Of 14 patients in group 1 who were less than 6 months of age at operation, 6 died in the early postoperative period (Fig.). All had a low cardiac output after operation up to the time of death.

The conduction abnormalities present before and after operation in the 2 groups are compared in Table 1.

Of the 39 children who underwent surgical correction of the ventricular septal defect through an atriotomy, 13 (33·3%) developed immediate postoperative complete right bundle-branch block, 14 (35·9%) left axis deviation, and 7 (17·9%) of these patients had combined complete right bundle-branch block and left axis deviation. Eleven (28·2%) patients had transient complete heart block during operation. Eight (20·5%) patients developed arrhythmias. Three children had a nodal rhythm and nodal ectopic beats immediately after operation, which were transitory. However, 2 children had atrial ectopic beats for 2 weeks and 1 month respectively, after operation. One child had atrial flutter coming off bypass and required defibrillation to convert to sinus rhythm. One child had first degree heart block and ventricular ectopic beats for 2 months after operation. One child had a wandering pacemaker.

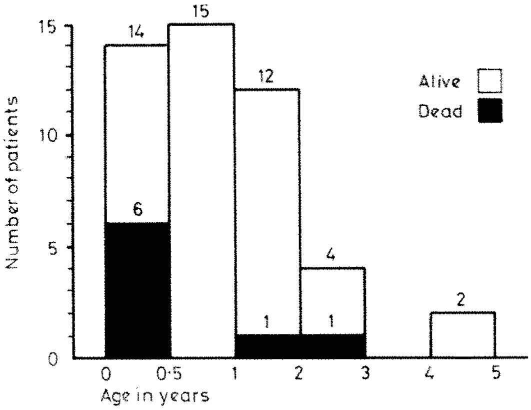

Fig. *Immediate operative mortality in children with ventricular septal defect repaired through a right atriotomy (group 1). The highest mortality occurred in infants less than 6 months of age.*

Further analysis of our data indicated that conduction disturbances occurred more frequently in infants less than 6 months of age than in children over 6 months. These figures are compared in Table 2. Left axis deviation occurred in 75 per cent of infants less than 6 months of age, compared with 25·8 per cent in children over 6 months of age (P < 0·03). Left axis deviation and complete right bundle-branch block occurred in 62·5 per cent of infants less than 6 months of age compared with 6·5 per cent of children over 6 months of age (P < 0·005).

In follow-up over a maximum of 3 years of all these patients with conduction disturbances and transient arrhythmias, there have been no further electrocardiographic changes and no further complications.

Table 1 *Postoperative conduction disturbances and arrhythmias in children with ventricular septal defect*

Surgical approach	*No. of patients*	*Complete right bundle-branch block*	*Left axis deviation*	*Left axis deviation + complete right bundle-branch block*	*Transient complete heart block*	*Left axis deviation, complete right bundle-branch block, and complete heart block*	*Arrhythmias*
Transatrial	39	13 (33·3%)	14 (35·9%)	7 (17·9%)	11 (28·2%)	2 (5·1%)	8 (20·5%)
Transventricular	19	15 (78·9%)	9 (47·3%)	8 (42·1%)	5 (26·3%)	3 (15·8%)	6 (31·5%)
		P < 0·001		P < 0·05			

Table 2 *Postoperative conduction disturbances and arrhythmias after repair of ventricular septal defect through the right atrium*

Age	*No. of patients*	*Complete right bundle-branch block*	*Left axis deviation*	*Left axis deviation + complete right bundle-branch block*	*Transient complete heart block*	*Left axis deviation, complete right bundle-branch block, and complete heart block*	*Arrhythmias*
< 6 months	8	5 (62·5%)	6 (75%)	5 (62·5%)	2 (25%)	1 (12·5%)	4 (50%)
> 6 months	31	8 (25·8%)	8 (25·8%)	2 (6·5%)	10 (32·2%)	1 (3·2%)	4 (12·9%)
			P < 0·03	P < 0·005			

GROUP 2

Fifteen (78·9%) children developed postoperative complete right bundle-branch block and 9 (47·3%) had left axis deviation. Combined complete right bundle-branch block and left axis deviation was present in 8 (42·1%) patients. Five (26·3%) children developed transient complete heart block during operation. One child had varying complete heart block for 4 days after operation. Six children (31·5%) developed arrhythmias. Four patients developed a junctional rhythm, 3 children had a transient arrhythmia, but 1 child developed the arrhythmia 1 year after operation. One child required a pacemaker for 10 days after operation, and went on to develop premature ventricular contractions, sinus arrest, and nodal escape beats in the 2 years after operation and required the implantation of a demand pacemaker at that time. Yet another patient who had no disturbances during operation developed ventricular ectopics for the first 6 months after operation, before returning to a normal rhythm.

Two children died in the early postoperative period of low cardiac output syndrome. One child died at home, but we have no further details.

Discussion

Pulmonary artery banding has been a standard life saving procedure for infants with large ventricular septal defects in whom vigorous medical treatment has failed to control symptoms. However, subsequent debanding and surgical repair of the defect may be difficult. Combined mortality for banding and subsequent total repair may be as high as 51 per cent (Kirklin *et al.*, 1976). Thus, single stage corrective surgery is attractive if morbidity and mortality are low.

Our initial experience with transatrial repair shows a mortality of 43 per cent in infants under 6 months of age and 3·6 per cent in children between 6 months and 2 years of age. There were 6 out of 14 patients in this subsection but only 1 had a complex lesion. If this patient is removed from our numbers, the mortality for less than 6 months of age for uncomplicated ventricular septal defect repair via an atriotomy is 35 per cent. Kirklin *et al.* (1976) reviewed published reports in which there was a similarly high mortality (33%) for this age group. There was no correlation between weight, surface area, preoperative symptoms, and duration of operation to account for this mortality figure. Another study from this hospital (Rowe and Trusler, 1977) confirms a mortality of 20 per cent in infants less than 1 year of age repaired via an atriotomy. Comparison of results of various surgical approaches is important to determine optimal repair. Conduction disturbances are a major consideration.

Ventricular septal defect repair via an atriotomy was first performed in our hospital in 1973. Thus, the maximum follow-up period for this group is only 3 years. Surgical correction through a right ventriculotomy has been carried out in selected patients since 1955. The presence of other associated cardiac abnormalities has influenced the decision of the approach and this fact is important in analysing our results.

Complete right bundle-branch block has been found to occur in 60 to 100 per cent (Kulbertus *et al.*, 1969; Gelband *et al.*, 1971; Okoroma *et al.*, 1975; Subramanian, 1976) of cases of ventricular septal defect repaired via a ventriculotomy. When a right atrial approach is used there is an incidence of 0 to 44·4 per cent (Gelband *et al.*, 1971; Okoroma *et al.*, 1975; Subramanian, 1976) of complete right bundle-branch block. Similarly, our results show a significantly reduced incidence of complete right bundle-branch block with an atriotomy of 33·3 per cent, compared with 78·9 per cent with a ventriculotomy ($P < 0{\cdot}001$). The incidence of left axis deviation occurring with complete right bundle-branch block was also statistically significantly reduced ($P < 0{\cdot}05$).

The mechanisms of production of complete right bundle-branch block electrocardiographic pattern with operation has been discussed extensively. Gelband *et al.* (1971) have implicated the incision through the ventricular muscle causing damage to the peripheral branches of the right bundle-branch. Coggin *et al.* (1960) and Massing and James (1972) share this view. Kaiser *et al.* (1970) have described an approach at the time of operation using an electrode probe to localise the specialised AV conduction pathways. This mapping technique requires a beating heart and is not adaptable to the child in whom circulation and cardiac arrest is required.

An alternative explanation which is applicable in at least a proportion of cases is direct injury to the main right bundle in its course over the edge of the membraneous ventricular septal defect. It is intimately related with the posteroinferior portion of such defects (Kirlin *et al.*, 1957; Lev, 1959, 1960; Titus *et al.*, 1963). This fairly constant relation of the bundle to the margin of the orifice seems to explain the high frequency of injury after surgical repair of the defect (Kulbertus *et al.*, 1969). The lesions have been shown to be due to suturing, manipulation, and hypoxia (Thung *et al.*, 1962), localised haemorrhage, traumatic disruption by suture, inflammation, or infarction (Titus *et al.*, 1963; Lev *et al.*, 1964).

Similarly, direct trauma explains injury to the right bundle and anterior branch of the left main bundle, producing electrocardiographic findings of complete right bundle-branch block and left axis deviation. Izukawa *et al.* (1971) and Godman *et al.* (1974) found that patients with this combination of injuries with a history of transient complete heart block in the immediate postoperative period were at risk for the development of late postoperative complete heart block. In our limited follow-up period of group 1 patients with this pattern, none developed late complete heart block or sudden death. There was 1 late sudden death in group 2, the full details of which are not known.

Our results show a reduced incidence of complete right bundle-branch block and left axis deviation with complete right bundle-branch block when the ventricular septal defect is repaired via a right atriotomy. The high incidence of complete right bundle-branch block after repair of the ventricular septal defect through a right ventriculotomy is probably the result of peripheral injury to the right bundle. The development of complete right bundle-branch block with left axis deviation after a ventricular septal defect repair through the atrium must be considered central in origin. The introduction of ventricular septal defect repair through the right atrium has statistically reduced the incidence of bifascicular block.

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Open heart surgery in first year of life using profound hypothermia (core cooling) and circulatory arrest[1]

Experience with 134 consecutive cases

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SUMMARY Between April 1970 and December 1977, 134 infants aged 2 days to 12 months underwent open heart surgery using profound hypothermia and total circulatory arrest. The technique of bypass (core) cooling is described. Results are reviewed for 4 principal diagnoses: 'simple' transposition of the great vessels, total anomalous pulmonary venous connection, ventricular septal defect, and Fallot's tetralogy. A mortality of 44 per cent in 32 cases during the first 3-year period has been reduced to 22 per cent in 102 cases during the subsequent 5 years. The overall mortality for the entire period was 28 per cent. The policy for the management of each diagnostic group is outlined.

The incidence of congenital heart disease is approximately 8 per 1000 live births (Rudolph, 1974). A third of this number of infants has critical congenital heart disease which leads to either cardiac investigation, surgery, or death (Nadas *et al.*, 1973). During the past decade, rapid and exciting progress has been made and early corrective surgery for the majority of patients has been advocated by many surgeons (Barratt-Boyes, 1973; Cartmill *et al.*, 1973; Venugopal *et al.*, 1973; Bailey *et al.*, 1976). This achievement results from improvements in the application of the techniques of profound hypothermia and cardiopulmonary bypass and advances in pre- and postoperative management. A simple method of bypass (core) cooling followed by circulatory arrest and bypass rewarming has been employed at the Royal Liverpool Children's Hospital since 1970 for the correction of congenital heart defects during the first year of life (Hamilton *et al.*, 1973). In this report, we outline this technique and present the results of our experience.

Method

Anaesthesia is induced with thiopentone and d-tubocurarine chloride and is maintained with nitrous oxide and oxygen (N_2O 4 l/min, O_2 2 l/min) to which carbon dioxide is added to give a final concentration of 2 per cent at temperatures above 35°C and 5 per cent below 35°C. Standard methods of monitoring are employed during and after operation. Supplementary doses of d-tubocurarine chloride and phenoxybenzamine (1 mg per kg intravenous) are given just before starting perfusion. The prime consists of 500 ml of fresh heparinised blood, 200 ml Hartmann's solution, 50 ml 5 per cent dextrose, and 3 ml 8·5 per cent sodium bicarbonate. Before perfusion, blood is maintained at a temperature of 37°C and is equilibrated with 95 per cent oxygen and 5 per cent carbon dioxide. The proportion of carbon dioxide is increased to 10 per cent at 30°C.

The Temptrol infant model Q130 oxygenator is used in conjunction with an infant heat exchanger in the arterial side of the bypass circuit. Perfusion is carried out at a rate of 2·4 l/min per m^2. A median sternotomy is used except for the correction of total anomalous pulmonary venous connection for which we favour a left anterolateral thoracotomy with trans-sternal extension. A short vertical pericardiotomy is made to expose only the upper part of the heart and the roots of the great vessels. This permits cannulation of the aorta and the right

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atrial appendage and maintains the normal position of the heart until perfusion is established. We believe that this reduces the likelihood of ventricular fibrillation which can result from kinking of the coronary arteries if the heart is allowed to tilt upwards when the pericardial sac is opened widely initially.

Once perfusion is established, the temperature of the perfusate is gradually reduced. A temperature differential of 10°C is maintained between the patient and the water circulating through the heat exchanger. A rate of cooling between 1 and 0·5°C per minute is achieved. Should the differential between nasopharynx and oesophagus exceed 5°C, the rate of cooling is reduced. During the cooling period, the pericardial sac is opened widely and the anatomy of the heart is studied. When the patient's temperature reaches the predetermined level, usually 18°C, perfusion is continued for a further 5 minutes at that temperature to reduce temperature gradients. This minimises the tendency for the temperature to drift upwards during the period of circulatory arrest. On average, the predetermined temperature is reached after 30 to 35 minutes of perfusion (core cooling).

At this stage, the arterial input is stopped, the line clamped, and the patient exsanguinated into the oxygenator via the right atrial cannula. The aorta and the pulmonary artery are occluded in a single clamp and the venae cavae are snared. During the period of circulatory arrest, blood in the oxygenator is maintained at the patient's body temperature. The intracardiac repair is completed within 45 to 60 minutes of circulatory arrest in the majority of cases. On the rare occasions when circulatory arrest is necessary for more than 70 minutes, a further short period of perfusion (5 to 10 minutes) is used before a second period of circulatory arrest. On completion of intracardiac surgery, rewarming perfusion is started by pressurising the arterial and venous systems. Air is removed from the aortic root by aspiration and from the left heart chambers via a left ventricular vent. When the patient's temperature reaches 30°C any base deficit or electrolyte imbalance is corrected. Rewarming is usually carried out at the same rate as cooling (0·5 to 1°C per minute). When the temperature reaches 34°C, perfusion is discontinued, provided that the cardiac output is adequate. Further rewarming is carried out by means of a water mattress beneath the patient. Usually, the rewarming period varies between 30 and 35 minutes.

Postoperatively, muscle relaxants are not reversed and the patients are ventilated through a nasotracheal tube connected to a square wave ventilator. The average period of ventilation is 30 hours.

Table 1 *Age distribution*

Age (mth)	*No. of patients*
0- 1	18
2- 3	30
4- 6	23
7-12	63
Total	134

Patients and results

During the period from April 1970 to December 1977, 134 infants in the first year of life underwent open heart surgery under profound hypothermia. There were 81 boys and 52 girls, ranging in age from 2 days to 12 months (mean 174 days); 71 were under 6 months of age (54%) (Table 1).

There were 4 principal diagnostic groups: simple transposition of the great vessels (31%), total anomalous pulmonary venous connection (19%), isolated ventricular septal defect (17%), and tetralogy of Fallot (9%). Less frequent diagnoses were pulmonary atresia with intact septum (7 patients) and aortopulmonary window (5 patients). Four patients had complex forms of transposition of the great vessels. There was also a miscellaneous group of 15 patients.

(1) 'SIMPLE' TRANSPOSITION OF GREAT VESSELS

Forty-two patients, 28 of whom were boys and 14 girls (mean age 6·3 months), had Mustard's

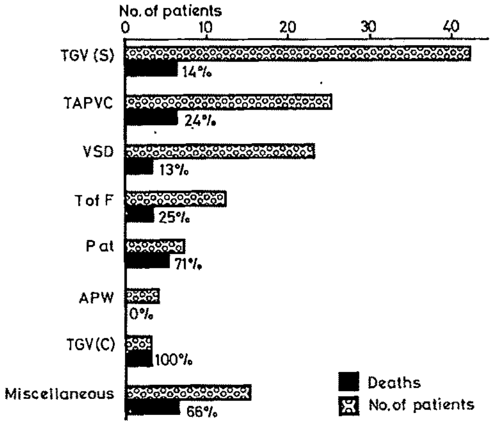

Fig. 1 *Hospital mortality related to type of cardiac defect (134 patients). TGV(S) = simple transposition of the great vessels; TAPVC = total anomalous pulmonary venous connection; VSD = ventricular septal defect; T of F = tetralogy of Fallot; P at = pulmonary atresia; APW = aortopulmonary window; TGV(C) = complex transposition of great vessels.*

Table 2 *Causes of hospital deaths after Mustard's operation for transposition of the great vessels*

Case no.	*Time of death*	*Cause*	*Postmortem findings*
1	1st day	Supraventricular arrhythmia	Satisfactory intracardiac repair
2	3rd day	Low cardiac output	Not available
3	10th day	Low cardiac output; renal failure; cerebral damage	Complete SVC obstruction due to organised thrombus
4	13th day	CHB low; cardiac output	IVC narrowed
5	5th day	Renal failure	Bilateral renal vein thrombosis
6	DOT	Sudden cardiac arrest	—

CHB, complete heart block; IVC, inferior vena cava; SVC, superior vena cava; DOT, death on the table.

operations using a pericardial baffle. There were 6 hospital deaths (14%) and 2 late deaths (Fig. 1). The causes of hospital death are shown in Table 2. The 2 late deaths were the result of pulmonary venous obstruction. One died 4 months later while awaiting a further operation and the other died 2 months later; necropsy showed pulmonary venous obstruction and bronchopneumonia.

Clinical follow-up for 3 months to 7 years after operation (mean 3·5 years) of 34 survivors (81%) shows that these children were progressing satisfactorily. Thirty-two patients were pink and fully active and 1 patient has minimal cyanosis at rest with exercise tolerance at the lower end of the normal range. Another patient required reinvestigation and reoperation 6 months later for pulmonary venous obstruction, and developed atrial flutter with 2:1 atrioventricular block and paralysis of the diaphragm. Four years later he was well despite some pulmonary venous obstruction. There was no clinical evidence of caval obstruction in the survivors.

Episodes of arrhythmia occurred in the immediate postoperative period in 16 of the 42 patients. Seven children remained in nodal rhythm with a satisfactory heart rate for periods varying from 24 hours to 7 days. One child had a sustained nodal tachycardia which reverted spontaneously to sinus rhythm after 36 hours. Junctional rhythm was present in 5 patients, 1 of whom died in the operating theatre without ever achieving an adequate cardiac output; 2 of the remaining 4 patients required temporary pacing. A further 2 patients had 2:1 heart block and also required pacing. One reverted to sinus rhythm after 7 days, but in the second the arrhythmia was probably a major contributing cause of death. All but 2 of the long-term survivors attending this hospital are in sinus rhythm. One child with nodal rhythm in the postoperative period now has first degree heart block (PR 0·24 s) and another who had complete heart block in the postoperative period now has a stable nodal rhythm.

(2) TOTAL ANOMALOUS PULMONARY VENOUS CONNECTION

Twenty-five infants (16 boys and 9 girls) (age distribution is shown in Fig. 2) underwent total correction. Fifteen had supracardiac, 3 had cardiac, 2 had the mixed type, and 5 had infracardiac drainage. There were 6 hospital deaths (24%) and no late deaths (Fig. 1). The youngest, a 5-day-old infant, survived correction of the infracardiac variety of

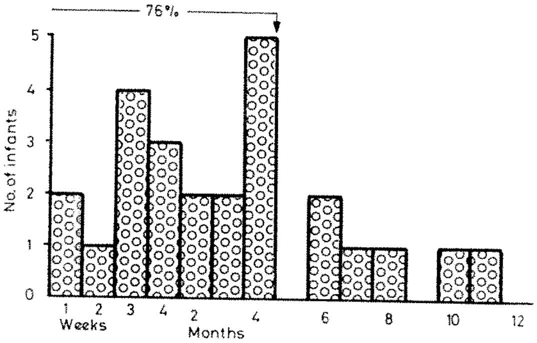

Fig. 2 *Age distribution of 25 infants with total anomalous pulmonary venous connection.*

Table 3 *Causes of hospital deaths after total correction of total anomalous pulmonary venous connection*

Case no.	*Type*	*Time of death*	*Cause*	*Postmortem findings*
1	Supracardiac	4th day	Extensive infarction of right lung	Good anastomosis
2	Infracardiac	DOT	Low cardiac output	Hypoplastic left heart chambers + aortic coarctation
3	Supracardiac	1st day	Low cardiac output	Hypoplastic left heart chambers
4	Mixed	DOT	Ventricular fibrillation (closing chest)	Not available
5	Cardiac	3rd day	Pulmonary oedema	Not available
6	Supracardiac	6th day	Severe cerebral damage	Diffuse brain softening

Table 4 *Causes of hospital deaths after patch closure of ventricular septal defect*

Case no.	*Associated anomalies*	*Time of death*	*Cause*
1	Multiple VSD and ASD (incomplete preoperative diagnosis)	48 hours	CHB; low cardiac output
2	ASD and PDA and LSVC to CS; peripheral branch PA stenosis (preoperative pneumonia not controlled)	4th day	Respiratory insufficiency
3	—	4th day	Low cardiac output

VSD, ventricular septal defect; ASD, atrial septal defect; PDA, persistent ductus arteriosus; LSVC, left superior vena cava; CS, coronary sinus; PA, pulmonary artery; CHB, complete heart block.

this lesion. The causes of death are summarised in Table 3. Mortality in infants with this lesion was not related to age, but rather to the anatomical type of venous connection. Follow-up from 5 months to 8 years (mean 3 years and 9 months) of 19 survivors (76%) shows that all of them are well and have normal exercise tolerance. One patient however, who had fits in the postoperative period, requires anticonvulsant therapy for convulsions with hyperpyrexia.

(3) VENTRICULAR SEPTAL DEFECT

There were 23 patients in this group, 12 boys and 11 girls. The mean age was 6·6 months. Three patients had associated atrial septal defect. Patch closure of the ventricular septal defect was affected via a right ventriculotomy in all cases. There were 3 hospital deaths (13%) and no late deaths. The causes of death are listed in Table 4.

(4) FALLOT'S TETRALOGY

Twelve patients, 6 boys and 6 girls, mean age of 7·0 months, had total correction, with 3 hospital deaths (25%) (Fig. 1). Gusset reconstruction was performed in 1 case. One patient died after failure of a pacemaker inserted for complete heart block at operation.

Another patient presented unusually in cardiac failure before operation and died after operation in a low cardiac output state. Necropsy showed myocarditis. A third patient died as a consequence of severe cerebral damage possibly as a result of intraoperative air embolism.

(5) OTHER LESIONS

Pulmonary atresia with intact interventricular septum

These infants underwent open heart surgery during the first week of life because of inadequate pulmonary blood flow. Five of these 7 patients died. When the pulmonary valve is thickened and the valve ring is of inadequate calibre, we have not met with success even when the valve tissue has been excised and a transannular gusset has been inserted. Under these circumstances and in the presence of hypoplasia of the right ventricle, we favour a combination of Rashkind's septostomy and a systemic-to-pulmonary arterial shunt (Waterston's anastomosis).

Table 5 *Miscellaneous group of infants who underwent totally corrective intracardiac surgery between April 1970 and December 1977*

Miscellaneous group	*No. of cases*	*No. of deaths*
Truncus arteriosus	1	0
Complete AV canal	2	2
Univentricular heart	1	1
Hypoplastic aortic arch and left ventricle	1	1
ASD (pulmonary hypertension)	2	0
Interrupted aortic arch (type B)	3	3
Tricuspid atresia	1	1
Cor triatriatum	1	1
Mitral regurgitation	1	0
Anomalous coronary artery	1	1
Aortic stenosis	1	0
Total	15	10

Five patients with *aortopulmonary window* all survived, and 4 patients with *complex forms of transposition of the great vessels* all died.

In the miscellaneous group, 2 infants aged 8 and 11 months had *atrial septal defects* with pulmonary hypertension. Both were failing to thrive. One suffered from recurrent pulmonary infections and the other from congestive cardiac failure which was resistant to medical treatment. Both had pulmonary artery pressures in excess of 50 mmHg. These infants had large ostium secundum defects which required patch closure; both survived. A 4-month-old baby with *truncus arteriosus* (*type II*) had a successful correction. No other patients with more complex lesions survived in this group (Table 5).

Summary of mortality

Thirty-seven patients died within 30 days of operation (28% hospital mortality). There were 2 late deaths (late mortality 1·5%). The distribution in each year of the patients operated on and the related hospital mortality is shown in Fig. 3. The hospital mortality of 44 per cent in 32 cases during the first 3 years has been reduced to 22·5 per cent in 102 cases during the subsequent 5 years. The

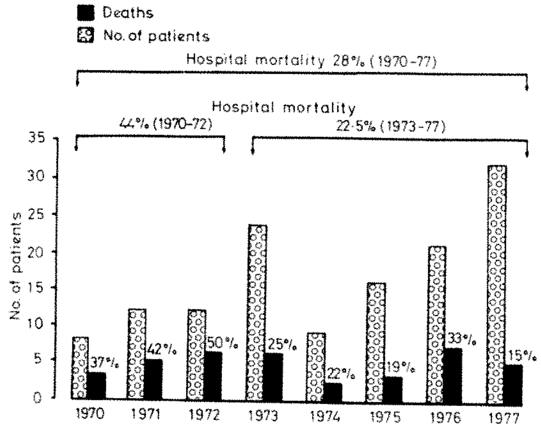

Fig. 3 *Annual distribution of patients and hospital mortality in 134 infants.*

hospital mortality was 50 per cent in the first month of life (mean age 10 days), 33 per cent in the second and third months of life (mean age 63 days), and 35 per cent at 4 to 6 months (mean age 141 days). The overall mortality rate for the group of patients operated on within the first 6 months was 38 per cent. The mortality over 6 months (mean age 9·8 months) was 17 per cent (Fig. 4).

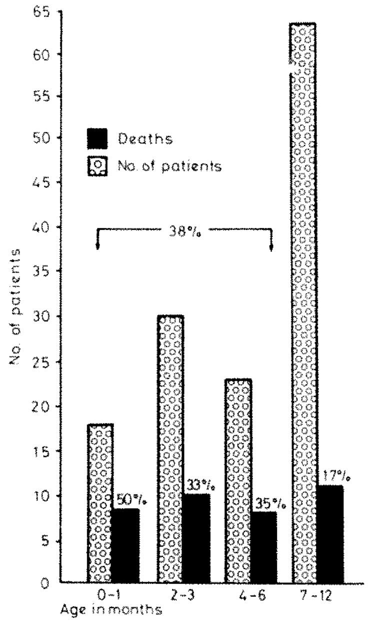

Fig. 4 *Age distribution and hospital mortality in 134 infants.*

Discussion

Although encouraging results using conventional cardiopulmonary bypass techniques for the correction of congenital heart disease in infancy have been reported (Gersony *et al.*, 1971; Breckenridge *et al.*, 1973; Bonchek *et al.*, 1974; Sugimura and Starr, 1977), the use of profound hypothermia seems more popular (Dillard *et al.*, 1971; Barratt-Boyes, 1973; Venugopal *et al.*, 1973; Castaneda *et al.*, 1974; Bailey *et al.*, 1976). A similar mortality and morbidity has been reported by Pooley *et al.* (1976) using standard cardiopulmonary bypass or profound hypothermia. Ischaemic cardioplegia gives the surgeon an ideal opportunity for performing accurate surgery on a motionless, relaxed heart in a bloodless field. By lowering the body temperature to 18°C, the period of tissue protection afforded even with complete ischaemia is at least 60 to 70 minutes (Barratt-Boyes, 1973). This offers the surgeon ample time to perform a totally corrective operation for many congenital defects. Comparative metabolic studies, using deep hypothermia by surface cooling and bypass cooling, have failed to establish the superiority of one or the other technique (Harris, 1973). Though deep hypothermia by surface cooling advocated by Hikasa *et al.* (1967) and Barratt-Boyes (1973) is more widely practised, our experience with perfusion induced profound hypothermia shows this to be safe even in the neonatal period.

Metabolic effects are within acceptable limits and there is a low incidence of cerebral complications. Postoperative convulsions occurred in 3 patients: 2 recovered, and 1 remains on anticonvulsant drugs. Two infants failed to regain consciousness and death was considered to be the result of air embolism caused by errors in surgical technique. Up to the end of 1973, the hypothermic technique we have described was used for all infants and children under 2 years of age who required open heart surgery. At the present time the technique is used for almost all infants under 1 year of age or 10 kg in weight and for selected cases between 1 and 2 years. Our experience suggests that profound hypothermia and circulatory arrest is particularly suitable for the correction of patients with total anomalous pulmonary venous connection and transposition of the great vessels.

A better knowledge of the pathophysiology and natural history of congenital heart diseases and the results of surgical treatment in infancy have enabled us to identify anomalies demanding early total correction. In our series, total anomalous pulmonary venous correction, simple transposition of the great vessels, symptomatic isolated ventricular septal

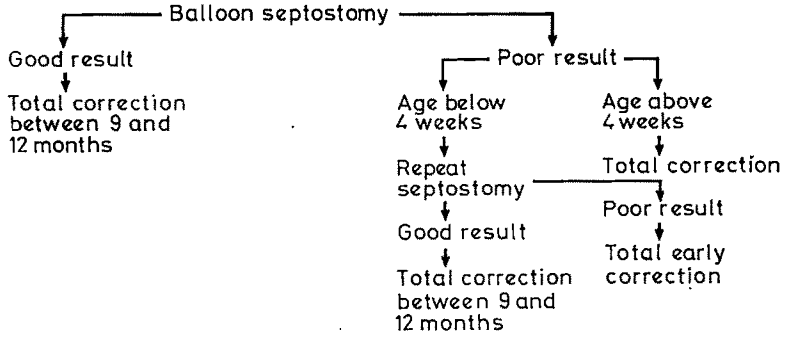

Fig. 5 *Current policy in the management of simple transposition of the great vessels.*

defect, and aortopulmonary window were the most common of these. The results of corrective surgery for total anomalous pulmonary venous connection are most encouraging and justify the policy of early correction, regardless of the age of the infant. Of 6 deaths in this group, 2 had very small left heart chambers at necropsy. Resistant pulmonary oedema was the cause of another death, though this complication has not been seen frequently in our series; the other deaths were related to technical errors and were, therefore, avoidable.

The management of infants presenting with simple transposition of the great vessels is becoming standardised throughout the world. Our policy is outlined in Fig. 5. The corrective procedure (Mustard's operation) is performed electively between the ages of 9 and 12 months. With the use of 4 to 6 ml balloon catheters for septostomy, it has seldom been necessary to consider open septectomy or correction before 9 months of age. Most of the deaths occurred early in our experience. In the last 25 consecutive cases, there has been 1 avoidable death.

The relatively small number of ventricular septal defects corrected under 1 year of age is explained by the fact that until 1974 banding of the pulmonary artery was employed in small babies in this clinic. Our current policy in the management of isolated ventricular septal defect with intractable cardiac failure and persistence or progression of pulmonary arterial hypertension is in favour of primary closure. We now reserve banding for multiple ventricular septal defects and for ventricular septal defect with associated anomalies (for example coarctation of the aorta). The presence of unsuspected multiple ventricular septal defect was the cause of 1 death. Accurate preoperative diagnosis of the anatomical site of the ventricular septal defect is of considerable importance as this may affect the surgical approach. Left ventricular cineangiography, to demonstrate the interventricular septum and any defect(s), is essential.

The successful outcome in the small group of patients with aortopulmonary window, who were in congestive cardiac failure unresponsive to medical treatment, justifies surgical intervention as soon as the diagnosis has been made. All 5 infants recovered uneventfully. One of these weighed only 2 kg at the time of operation.

Many infants with Fallot's tetralogy reach the age of 3 to 4 years without surgical intervention. Total correction is performed using conventional bypass techniques at that age. Primary early correction versus staged treatment continues to be the subject of debate. Our present policy is in favour of early total correction in the presence of cyanotic spells, if the diameter of the pulmonary arteries is adequate and the pulmonary valve ring is at least half the diameter of the ascending aorta. Where there is gross disproportion between the great vessels, we favour a pulmonary to systemic shunt, because we prefer to avoid the use of gusset reconstruction of the right ventricular outflow and pulmonary valve ring in infants with tetralogy. In our experience, pulmonary regurgitation is not well tolerated in the early postoperative period and we prefer to reconstruct severely restrictive outflow tracts after the age of 4 years by grafting a complete (tri-leaflet) aortic homograft into the right ventricular outflow tract and main pulmonary artery. The survivors after total correction in infancy are progressing well, though the follow-up time is still too short for a definitive judgement. Complete heart block, with fatal outcome, occurred in 1 patient with Fallot's tetralogy.

Complex forms of transposition of the great vessels, pulmonary atresia with intact septum, and most of the conditions listed in the miscellaneous group (Table 5) for which both early total correction and palliative operations are followed by high mortality, represent the frontier of paediatric cardiac surgery and still present a formidable challenge to cardiologists and surgeons. Successful complete repair of truncus arteriosus in a 4-month-old infant encourages us to pursue an aggressive surgical approach to this abnormality in the future.

Conclusions

Our experience in the management of critically ill infants with congenital heart disease leads us to the following conclusions.

(1) The ability to perform the complete repair of congenital heart defects in infancy is a significant advance. One method of achieving this is by the use of profound hypothermia and circulatory arrest which enables the surgeon to work on a relaxed heart in a bloodless field. This has enlarged the scope of surgical intervention, both in terms of early primary total correction and open heart palliative treatment.

(2) Earlier referral and complete diagnosis, adequate preoperative preparation, and improved surgical technique and postoperative management of these infants has been paralleled by a significant lowering of the surgical mortality.

The mortality for total correction in the neonate is double that for the infant of 6 months of age. It is our policy, therefore, to delay total correction if the clinical condition allows. In the case of total anomalous pulmonary venous connection and aortopulmonary window, however, mortality is unrelated to age and total correction is advised as soon as the diagnosis is made.

(3) The neonate and infant tolerate open heart surgery remarkably well. Whenever it has been possible to perform a complete or nearly complete anatomical repair, without the creation of complete heart block, a satisfactory result has seldom been in doubt. Complex repairs, provided they fulfil these criteria, can be equally successful.

(4) It is likely that in the future the surgical treatment of congenital heart disease will more often be performed during infancy and the first few years of life. Expertise in many disciplines and close co-operation between them is essential for success. The relatively constant annual workload in this field justifies the concentration of specialist skills in several disciplines within a limited number of properly equipped and adequately staffed units.

(5) The longer term follow-up of children who have undergone totally corrective cardiac surgery is awaited with interest. So far, results are highly encouraging as the majority of children, including those treated surgically in the neonatal and infant age range, are leading active lives and are attending normal schools. Many have no residual disabilities related to the cardiovascular system.

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Poor response to oral indomethacin therapy for persistent ductus arteriosus in very low birthweight infants

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SUMMARY Administration of oral indomethacin to treat cardiorespiratory failure in 7 low birthweight infants, after failure of conventional therapy, produced an improvement in only 2 infants. These infants had a higher birthweight than the group as a whole. Surgical ligation, rather than oral indomethacin, may be the treatment of choice for persistent ductus arteriosus in very low birthweight infants.

In view of the increasing frequency of persistent ductus arteriosus in neonatal special care units, there has been an increased interest in methods of duct closure. The recent introduction of pharmacological techniques of duct closure by means of indomethacin has led to its widespread use in this condition, in order to avoid surgical ligation as a method of treatment (Friedman *et al.*, 1976; Heymann *et al.*, 1976). However, complications from the use of such drugs have been recorded, and other theoretical risks suggested (Nadas, 1976). In addition, the initial success rate for treatment with indomethacin has not always been supported by studies from other centres (Neal *et al.*, 1977). We report our own experience with indomethacin therapy for persistent ductus arteriosus in low birthweight infants over the past 18 months.

Methods

Diagnosis of a left to right shunt through a persistent ductus arteriosus was made on clinical grounds, by the presence of a characteristic systolic murmur, together with a wide pulse pressure, radiological evidence of pulmonary plethora, and usually an increase in diameter of the cardiac shadow (Jones and Pickering, 1977). Conventional therapy with digoxin, frusemide, and restriction of fluid intake to less than 150 ml/kg per day was begun if failure occurred. Failure was defined as increasing requirement for oxygen or respiratory support, or as cardiac failure as evidenced by liver enlargement, tachycardia, and/or excessive weight gain. Constant positive airway pressure was usually used to treat recurrent apnoea, which was a common problem if the infant was not ventilated (Roberton, 1974). If clinical improvement did not occur, surgical ligation was performed, and carried a low operative mortality (Cooke *et al.*, 1978). Nevertheless, there was frequently a reluctance to subject small infants to surgery at an early stage as prolonged supportive measures may result in spontaneous recovery, even in severe cases (Roberton, 1974).

However, if such measures include ventilation, infants may die from chronic lung disease before recovery from persistent ductus arteriosus occurs (Nelson *et al.*, 1976; Cooke *et al.*, 1978). To avoid such a situation, indomethacin therapy has been tried before ligation of the ductus in 7 infants.

After at least 48 hours of digoxin and diuretic therapy, with respiratory support as required, indomethacin was administered if no clinical improvement had occurred. 0·2 mg/kg per dose was given via a nasogastric tube at 12-hourly intervals for 3 doses. One infant (case 1) had only one dose because of pronounced oliguria. Surgical ligation was carried out if no improvement occurred after 3 doses of indomethacin.

Results

Seven low birthweight infants received treatment with indomethacin (Table). All had been ventilated for moderate to severe hyaline membrane disease, and 3 infants were still receiving ventilation at the time of treatment (cases 1, 5, and 7). Mean gesta-

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Table *Course of illness treated by oral indomethacin*

No.	*Early illness*	*Gestation (wk)*	*Birth-weight (g)*	*Time murmur first heard*	*Time of ductus 'failure' developing*	*Age when indomethacin started*	*Result*	*Outcome*
1	HMD	25	790	7 days	8	27	No response; oliguria 1d	Duct ligated 46d; died 127d; bronchopulmonary dysplasia
2	HMD	32	1340	11 days	21	24	No response	Duct ligated 29d; did well
3	HMD	29	1200	4 days	27	32	No change; oliguria 1d	Duct ligated 35d; did well
4	HMD	30	1120	3 days	9	16	No response	Duct ligated 19d; did well
5	HMD	28	1140	4 days	4	15	No response	Duct ligated 49d; died 69d; bronchopulmonary dysplasia
6	HMD	30	1440	8 days	21	23	Symptoms/signs reduced after 1 dose; off all therapy after 4d	Continued to do well
7	HMD	34	2080	9 days	18	21	Symptoms/signs reduced after 3rd dose; off all therapy after 4d	Continued gradual improvement complicated by bronchopulmonary dysplasia

HMD, hyaline membrane disease; d, day.

tional age was 29·7 weeks (range 25 to 34 weeks) and mean birthweight 1300 g (range 790 to 2080 g). The ductus murmur was heard at a median age of 7 days, and failure occurred at a median age of 18 days. Indomethacin was given at a median of 5 days after failure. No response was noted clinically in 5 out of 7 infants. Oliguria occurred in 2 infants, but they recovered within 24 hours. Of the 5 infants in whom indomethacin therapy failed, all had surgical ligation of the ductus, 2 died subsequently at 69 and 127 days from bronchopulmonary dysplasia, probably as a consequence of prolonged mechanical ventilation in the presence of pulmonary plethora. All the other infants survived and did well. In the 2 infants who showed a response to indomethacin (cases 6 and 7), the murmur of persistent ductus arteriosus, though reduced in intensity, persisted in both infants. Other symptoms and signs were much reduced, however, and both infants were off all treatment at 4 days after the start of indomethacin treatment. Case 7 subsequently had a recovery prolonged by chronic lung disease, but did well.

Discussion

In previous published work on the use of indomethacin in the treatment of persistent ductus arteriosus in low birthweight infants, results have been very good, with successful closure of the duct in most if not all cases (Friedman *et al.*, 1976; Heymann *et al.*, 1976); with higher doses of indomethacin than used in our unit, renal failure was common (Friedman *et al.*, 1976; Heymann *et al.*, 1976). In the series reported in this paper, only 2 out of 7 infants avoided surgery because of a response to indomethacin therapy. In these 2 infants, the signs of persistent ductus arteriosus did not disappear completely, but supportive therapy could rapidly be discontinued. Both infants were relatively more mature and of greater birthweight than the group as a whole, and no infant of less than 30 weeks' gestation and 1400 g birthweight responded to indomethacin therapy. In the series of Friedman *et al.* (1976) all infants were over 1050 g birthweight, with an average birthweight of 1500 g, and so comparable with the 2 infants successfully treated in this series. Heymann *et al.* (1976) included several infants of below 1000 g in their group of successfully treated infants, but full details of infants in a more extensive study are not available (Heymann and Rudolph, 1977).

The time of administration of indomethacin may be important, as postnatal age and the duration of patency of the ductus may alter its response. We gave the drug relatively late, at between 11 and 28 days after the first clinical signs of the ductus appeared, at a postnatal age of 15 to 32 days. This is considerably later than the time of administration in other series such as that of Heymann *et al.* (1976). When observed at operation, the ducts that failed to close were of large diameter and thin walled, and it was not difficult to attribute the failure of closure to lack of muscular tissue in the duct wall. It is not possible to say for certain whether this was an acquired feature, but it does seem probable.

In conclusion, it seems that indomethacin may not prove useful in the treatment of very low birthweight infants with persistent ductus arteriosus, at least at a late stage of the illness. In larger infants who develop cardiorespiratory failure secondary to persistent ductus arteriosus, a trial of indomethacin therapy may avoid the necessity of surgical ligation.

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Failure of indomethacin to close persistent ductus arteriosus in infants weighing under 1000 grams

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SUMMARY Six preterm infants with a persistent ductus arteriosus, who failed to improve with conventional medical management, received indomethacin in an attempt to close the duct pharmacologically. All infants weighed less than 1000 g when the drug was administered. All showed a transient response to indomethacin; however, no infant demonstrated a permanent response, even though 5 of the 6 received multiple doses. One of the patients developed a severe episode of anuria, uraemia, and gastrointestinal bleeding. Of the 6 infants, 3 underwent subsequent successful surgical ligation of the ductus. It is suggested that the extremely preterm infant may be a 'poor responder' to indomethacin. Since the side effects of indomethacin may be life-threatening, it may be wise to consider surgical ligation *in lieu* of indomethacin administration in these infants.

Management of persistent ductus arteriosus in preterm infants has been the subject of much research, discussion, and debate (Zachman *et al.*, 1974; Neal *et al.*, 1975; Thibeault *et al.*, 1975). Until recently, if medical management failed, the only alternative was surgical ligation. In September 1976, the successful use of indomethacin, a potent prostaglandin synthetase inhibitor, was reported as promoting pharmacological closure of the persistent ductus arteriosus (Friedman *et al.*, 1976; Heymann *et al.*, 1976). The possibility of avoiding surgery in tiny preterm infants has led to the use of indomethacin in many institutions. However, in view of the possibility of side effects, several investigators have cautioned against widespread use of prostaglandin inhibitors before carefully designed clinical trials (Nadas, 1976; Friedman *et al.*, 1977). Review of the data from 6 preterm infants who received the drug in the past 8 months forms the substance of this report.

Subjects and methods

PATIENT POPULATION

Between November 1976 and June 1977, preterm infants with persistent ductus arteriosus were considered as candidates for the administration of indomethacin according to the following guidelines.

All preterm infants with clinical features thought to be secondary to a persistent ductus arteriosus, with or without respiratory distress syndrome, received a trial of medical management for 48 hours. This included digitalis, diuretics, and careful fluid management. Failure of medical management was defined as continued severe congestive heart failure and/or inability to wean the infant from respiratory support (including constant positive airway pressure). In such cases, indomethacin was administered to those preterm infants who weighed less than 1000 g. Preterm infants who weighed more than 1000 g underwent prompt surgical ligation of the persistent ductus arteriosus.

The diagnosis of persistent ductus arteriosus was based on typical physical, electrocardiographic, radiological, and echocardiographic findings.

Indomethacin was administered as a single dose of 0·3 mg/kg through a nasogastric tube. If there was no closure of the ductus within 48 hours (as manifested by disappearance of murmur, improvement in congestive heart failure, and discontinuance of respiratory support), surgical ligation was considered. If there was a response which was then followed by a relapse, a second dose of 0·3 mg/kg was administered since the persistent ductus

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arteriosus presumably was responsive to indomethacin.

Results

From November 1976 to June 1977, 6 infants, each weighing less than 1000 g, received indomethacin. Clinical details are presented in the Table. The mean gestational age of the infants who received indomethacin was 29 weeks. The mean age at which the signs of persistent ductus arteriosus were first noted was 10 days, with a range of 5 to 30 days of age. Four of the 6 infants required respiratory assistance at the time the diagnosis of persistent ductus arteriosus was made. One infant required mechanical ventilation for his primary pulmonary disease and 3 required constant positive airway pressure for apnoea. All 6 infants were receiving maintenance digitalis, intermittent diuretics, and had their fluids restricted to 120 to 150 ml/kg per 24 hours. Two infants received aminophylline for treatment of recurrent apnoea within 48 hours of the administration of indomethacin.

All 6 infants exhibited the classical clinical signs of persistent ductus arteriosus, including typical murmur, gallop rhythm, full pulses, and hepatomegaly. Additionally, all infants had cardiomegaly and increased pulmonary vascularity on chest *x*-ray examination.

All infants had a transient beneficial response after the administration of indomethacin. This consisted of a decrease in the intensity of the murmur and of the peripheral pulses 6 to 12 hours after the administration of indomethacin. In all 6 infants, however, this response was short-lived, lasting approximately 12 hours. Treatment was repeated in 5 infants (5 doses in 1 case, and 3 in another), but in no case was permanent closure of the duct achieved with indomethacin.

Three of the 6 infants subsequently underwent surgical ligation of the duct. These 3 infants were in intractable congestive heart failure and, though critically ill, it was felt that the risk of congestive heart failure and its attendant problems outweighed the risk of surgery. All 3 infants survived surgery, had relatively benign postoperative courses, and showed complete resolution of congestive heart failure. Three infants did not undergo surgical ligation of the duct, as their congestive heart failure was relatively well controlled by medical management alone. Maintenance digitalis was continued at the time of discharge in 1 of these infants.

Side effects thought to be related to indomethacin were noted in case 6. This patient was a preterm infant requiring constant positive airway pressure for apnoeic spells. She received indomethacin on the seventh day of life, 0·3 mg/kg by oroduodenal tube. Within 12 hours after this dose was administered, her murmur decreased slightly in intensity and her peripheral pulses decreased in amplitude. This effect lasted for approximately 18 hours, at which time her murmur increased in intensity and clinical signs of congestive heart failure increased. A repeat dose of indomethacin (0·3 mg/kg) was given by oroduodenal tube on the eighth day of life. Within 24 hours, she was anuric. Her congestive heart failure

Table

Case no.	*Gestational age (wk)*	*Birthweight (g)*	*Associated diagnosis and support*	*Age PDA noted (d)*	*Indomethacin*			*Response*	*PDA closure*	*Side effects*	*Outcome*
					Age (d)	*Route*	*Dose (mg/kg)*				
1	31	1000	CPAP and aminophylline for apnoea	5	13 14	Rectal	0·3 0·12	Transient None	Spontaneous at 6 wk	None	Survived
2	28	810	CPAP and aminophylline for apnoea	7	27	NG tube	0·3	Transient	Spontaneous at 6 wk	None	Survived
3	34	1050	Respiratory distress syndrome and apnoea	6	11	NG tube	0·3 0·3	Transient Transient	No Discharged on digoxin	None	Survived
4	28	860	Apnoea	30	30 31 32	NG tube	0·2 0·3 0·3	Transient None None	Surgical at 35 days	None	Survived
5	26	720	Respirator for bronchopulmonary dysplasia and apnoea	5	30 31 33 37 42	NG tube	0·3 0·3 0·3 0·3 0·3	Transient Transient Transient None None	Surgical at 56 days	None	Died day 90 from necrotising enterocolitis
6	28	890	CPAP for apnoea	5	7 8	NG tube	0·3 0·3	Transient None	Surgical at 12 days	Renal failure and GI bleeding	Survived

PDA, persistent ductus arteriosus; NG, nasogastric; CPAP, constant positive airway pressure; GI, gastrointestinal.

was exacerbated, and she required intubation and respirator support. Her creatinine rose to 362 μmol/l (4·1 mg/100 ml) and her blood urea rose to 31·0 mmol/l (87 mg/100 ml) on day 12. Additionally, she developed bloody stools for 24 hours. On day 12 of life, she underwent surgical ligation of her duct with some resolution of her symptoms. Her urine output began to increase in approximately one week. She subsequently was weaned from the ventilator, and her creatinine returned to a normal value in 24 days. She was discharged with no medication. The indomethacin used in this child was tested[1] and found to be the appropriate concentration as labelled by the University of Virginia Hospital Pharmacy. We found no error in the administration of this drug when reviewing hospital charts and nursing records.

Discussion

Published reports, with one exception (Neal *et al.*, 1977), have been enthusiastic concerning the use of indomethacin for the pharmacological closure of the persistent ductus arteriosus. In the study by Friedman *et al.* (1976), 6 preterm infants with respiratory distress syndrome and persistent ductus arteriosus responded to a single dose of indomethacin. The dosage used in this study was 2·5 mg/kg by mouth or 5 mg/kg per rectum. The only side effects noted were transient reduction in renal function in 2 infants. Heymann *et al.* (1976), using a much lower dosage of indomethacin (0·1 to 0·3 mg/kg), also felt indomethacin to be a valuable drug for producing constriction of the persistent ductus arteriosus. In their study, complete closure occurred within 24 hours in 5 infants given 0·3 mg/kg. Two of these infants received 3 doses, and a raised serum creatinine was noted for 1 week. A very low dose, 0·1 mg/kg, of indomethacin was used in 10 infants; ductal closure occurred within 24 to 30 hours in 8, and no alteration in renal function was noted. Heymann and Rudolph (1977) have subsequently published, in abstract form, data from an expanded trial, which apparently support their earlier findings, though it is unclear whether a 'response' was meant to indicate permanent or transient closure of the duct.

Our experience differs from these previously reported data, since none of our 6 preterm infants had a permanent response to indomethacin administration. Though we did observe transient responses, which were dramatic at times, this response was not sustained despite multiple doses. There are several possible reasons for the lack of permanent response in our infants. It has been suggested that there is inadequate development of the smooth muscle in the ductus arteriosus in the preterm infant (Danilowicz *et al.*, 1966). Since all of our infants were premature (mean gestational age 29 weeks, with birthweights ranging from 720 to 1050 g), it is quite possible that there was insufficient musculature to produce sustained constriction in response to either oxygen or indomethacin. The birthweights of all infants studied by Friedman *et al.* were over 1050 g, with a mean weight of approximately 1500 g. The group studied by Heymann *et al.*, however, included 5 infants weighing less than 1000 g. Four of these infants responded to indomethacin with permanent ductal closure, and, of these responders, only 1 required a repeat dose (0·1 mg/kg × 2).

In previous studies the responsiveness of the duct to pharmacological closure has not been related to the postnatal age at which indomethacin was administered. These data are not available in Friedman's study. However, the mean age at which indomethacin was administered in Heymann's study was 10 days, with a range of 4 to 21 days. The mean age in our infants was 20 days, with a range from 7 to 30 days. Data from Olley *et al.* (1976) indicate that the ductus of preterm lambs will respond to blockers of prostaglandin synthesis at an early fetal age; however, there are no data concerning the responsiveness of the duct at particular postnatal ages in these same preterm animals. Since the ductus appears to lose sensitivity to oxygen as postnatal age increases (Nelson, 1976), it seems possible that the duct similarly might be less responsive to pharmacological agents later in the course of the infant's disease.

There is no comment in the previous papers as to whether or not the infants were receiving other medications, such as aminophylline. Many infants with persistent ductus arteriosus are also being treated for recurrent apnoea and may receive xanthines as part of such treatment (Shannon *et al.*, 1975; Uauy *et al.*, 1975). Two infants in our group had received aminophylline less than 48 hours before the administration of indomethacin. Theoretically, aminophylline might pharmacologically inhibit the effects of indomethacin on ductal closure. Aminophylline relaxes ductal tissue *in vitro*, presumably by increasing cyclic AMP (Kreil *et al.*, 1973). It has been suggested, however, that the doses of aminophylline required to open the duct *in vivo* would be far in excesss of those doses currently in use for the treatment of apnoea (Soyka and Heese, 1975).

The lack of permanent response in our patient population is disconcerting as the use of indomethacin was initiated in an attempt to avoid surgery and its attendant risks in the tiny, preterm, critically ill infant. However, the risks of the drug also seem to be significant. Reported side effects of the drug include gastrointestinal toxicity, hepatitis, blood dyscrasias (Goodman and Gilman, 1970), and a deterioration in renal function (Friedman *et al.*, 1976; Heymann *et al.*, 1976). One of our infants (case 6) had a severe and potentially life-threatening episode of anuria and gastrointestinal bleeding temporally associated with the administration of indomethacin. Additionally, 3 of the infants in whom indomethacin was administered in an effort to avoid surgery ultimately required surgical ligation of the duct. Surgery was very well tolerated in all 3 patients, there were no complications, and the clinical response to surgical ligation was excellent.

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[1] Courtesy of Dr E. M. Cohen, Merck Sharp & Dohme Research Laboratories, West Point, Penn. 19486, USA.

Thus, in our experience, the ductus of the small preterm infant does not appear to respond well to indomethacin administration. Moreover, since the incidence of the side effects of indomethacin is unknown and the risk of surgical ligation appears relatively low, we feel it may be wise to consider early surgical ligation in preference to pharmacological treatment in these infants.

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Arterial counterpulsation in severe refractory heart failure complicating acute myocardial infarction

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SUMMARY The role of arterial counterpulsation was sought in 100 patients with severe refractory cardiac failure complicating myocardial infarction. Seventy-four were in shock and 26 were not. Average duration of counterpulsation was 7·0 days. Hospital survival was 34 per cent (25/74) in shock (predicted $< 10\%$) and 65 per cent in patients who were not in shock (predicted $< 50\%$). Survival at 4 years was 10 ± 4 per cent in shock and 37 ± 11 per cent in patients not in shock; functional status was class 1 or 2 in 5 of 9 patients in shock and in 8 of 12 survivors not in shock. Results were best when counterpulsation was started early after onset of symptoms, when ischaemic pain was still present, or when a mechanical defect was corrected surgically. Early coronary artery bypass surgery performed alone in 9 patients did not influence survival or functional status. Complications of counterpulsation occurred in 17 patients in shock and in 2 patients not in shock, all but 6 on the first day; none directly caused death. Counterpulsation is an effective and safe adjunct to medical treatment of complicated infarction provided the intervention is prompt.

Ten years after the first application of intra-aortic balloon counterpulsation in man (Kantrowitz *et al.*, 1969) there is still no consensus as to its role in the management of acute myocardial infarction. Physiological principles concerning the left ventricle's demand for and supply of blood (Sarnoff *et al.*, 1958; Berne, 1964) strongly suggest that such a role exists, as do experimental findings in animals with myocardial ischaemia and early infarction (Soroff *et al.*, 1963; Brown *et al.*, 1967; Goldfarb *et al.*, 1968; Powell *et al.*, 1970; Maroko *et al.*, 1972). However, in the 2 clinical syndromes of acute coronary disease with which most experience has been obtained—cardiogenic shock on the one hand and coronary insufficiency on the other—many published results show little benefit over conventional therapy (Scheidt *et al.*, 1973; Forrester *et al.*, 1976; Mundth, 1976). Furthermore, where benefit has been evident, counterpulsation has often been combined with coronary artery bypass surgery so that its own role has remained uncertain (Dunkman *et al.*, 1972; Sanders *et al.*, 1972; Leinbach *et al.*, 1973; Miller *et al.*, 1974; Willerson *et al.*, 1975; Bardet *et al.*, 1977; Erich *et al.*, 1977).

We report here our experience with the first 100 patients with acute infarction who were treated with counterpulsation over a 5-year period. These patients were accepted from a group of over 300 referred for consideration of mechanical heart assistance (O'Rourke *et al.*, 1975, 1976).

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Criteria and procedure

In the first 8 months of this project (November 1971 to July 1972), we followed strictly the procedure adopted at the Massachusetts General Hospital (Dunkman *et al.*, 1972; Sanders *et al.*, 1972); we reserved counterpulsation for patients who met the strict MIRU criteria of cardiogenic shock (Dunkman *et al.*, 1972) and subjected all patients on counterpulsation to coronary angiography within the first 48 hours with a view to early coronary artery bypass surgery. Results at this stage were dismal (O'Rourke *et al.*, 1975). We attributed these poor results to the unrealistically strict definition of shock, to the delays incurred in preliminary assessment, and to the trauma of cardiac diagnostic and surgical procedures. We, therefore, developed a different procedure which we have followed strictly over the latter part of this project.

Our present procedure requires (1) a diagnosis of definite acute myocardial infarction by WHO criteria (WHO, 1970), (2) definite evidence of acute severe heart failure by clinical and radiological criteria (WHO, 1970), or (if such signs are equivocal) an increase in pulmonary artery pressure above 16 mmHg wedge or 20 mmHg mean, and (3) absent or completely unsatisfactory response to medical treatment over at least a 2-hour period, such treatment to include oxygen by mask, relief of pain, adequate diuretics (the minimum dose of frusemide was 80 mg by intravenous injection), and correction of haemodynamically significant arrhythmias. The MIRU definition of cardiogenic shock (Dunkman *et al.*, 1972; Sanders *et al.*, 1972; O'Rourke *et al.*, 1975) was modified by (a) foregoing the requirement of pulmonary and systemic catheterisation before counterpulsation if clinical signs of cardiac failure were unequivocal and if indirect pressure in the brachial artery was less than 100 mmHg systolic and (b) allowing urine output up to 25 ml/hour with diuretic therapy. All other aspects of the 'MIRU definition' (Dunkman *et al.*, 1972) were retained.

Our present procedure requires that diagnostic cardiac catheterisation and coronary angiography be performed only if (1) a mechanical complication is suspected, (2) a patient cannot be weaned from counterpulsation after 2 weeks, or (3) angina pectoris recurs after counterpulsation is terminated. The procedure no longer includes consideration of early coronary artery bypass surgery. The procedure requires that counterpulsation be continued until maximal clinical improvement has been attained and maintained for at least 3 days. At this stage (usually after 7 to 10 days), a trial of weaning is performed (O'Rourke *et al.*, 1975). If deterioration occurs, counterpulsation is continued for a further 4 to 7 days and the trial repeated. If no deterioration occurs, the balloon catheter is removed.

Avco catheters and consoles were used throughout. The balloon catheter was inserted through a 'dacron' side graft into the femoral artery (Kantrowitz *et al.*, 1968). Monitoring catheters were placed in the pulmonary and brachial or radial artery of all patients. In the interests of expediency this procedure was usually done at the same time as the surgical team was cannulating the femoral artery. Heparin (usually 5000 international units intravenously, 4 hourly) was administered to all patients except those undergoing cardiac surgery; and these were given low molecular weight dextran (10 ml/hour) during operation instead. Cephalothin (0·5 g intravenously, 6 hourly) was administered routinely. Drug treatment for heart failure was continued but adjusted when improvement occurred.

In this study, contraindications to counterpulsation were similar to those applied by others (Dunkman *et al.*, 1972; Sanders *et al.*, 1972), and included age > 70, pre-existing uncontrolled heart failure, severe symptomatic peripheral vascular disease, severe intercurrent disease, and aortic regurgitation.

No patient was lost to follow-up (which was done by personal interview and examination in all but one survivor), 1 to 52 (mean 24) months after discharge.

Patients

Seventy-four patients were in cardiogenic shock (Table 1) and 26 were not (Table 2). The 74 in shock comprised 58 with myocardial power failure alone and 16 with a mechanical complication which caused or contributed to shock. Fourteen of the 16 mechanical complications were a consequence of myocardial disruption (Table 3). There was only one mechanical complication (ventricular pseudoaneurysm) in the group of patients without shock. Most patients had been transferred from other hospitals, a factor which explained in part the long delay (median 24 hours for patients in shock and 34 hours without) between onset of symptoms and initiation of counterpulsation. Age (mean 55 and 53), incidence of previous infarction (approximately 1 in 3), heart rate (110 and 118 beats/min), and pulmonary artery pressure (mean 34 and 32 mmHg) were similar in the groups with and without shock.

Predicted survival rate for patients with shock was < 10 per cent (Wan *et al.*, 1971; O'Rourke *et al.*, 1975; O'Rourke, 1977) and for patients without shock was < 50 per cent from Peel *et al.* (1962) and Norris *et al.* (1969) indices (Table 2). Of the first 200 patients referred to us for consideration of counterpulsation, 39 met the criteria but did not proceed to counterpulsation. Of these, only 2 (5%) (including 1 patient who was not in shock) were hospital survivors.

Results

(a) PATIENTS IN CARDIOGENIC SHOCK

Initiation of counterpulsation was associated with clinical improvement in the majority of patients. Relief was manifest in reduction of mean pulmonary artery pressure and heart rate from 34 ± 10 mmHg and 110 ± 22/min to 26 ± 10 mmHg and 98 ± 17/min, respectively, by the end of the first day ($P < 0{\cdot}001$ for each by paired t test). Deterioration during counterpulsation was seen only in patients who remained in shock or acute renal failure despite counterpulsation and in those undergoing early trials of weaning, angiography, and cardiac surgery. Deterioration after termination of counterpulsation was, however, common.

Table 1 *Patients with cardiogenic shock*

	Group A *(myocardial power failure only)*	*Group B* *(mechanical complications)*
No.	58	16
Male/female	47/11	9/7
Age (y)	$\overline{54}$ (37-66)	$\overline{59}$ (48-66)
Previous infarction	23	2
Referral from other hospital	43	12
Heart rate before counterpulsation	110 ± 22/min	108 ± 22/min
Systemic pressure before counterpulsation* (mmHg)	77/56 ± 16/6	79/63 ± 10/14
Pulmonary artery mean pressure before counterpulsation† (mmHg)	36 ± 10	30 ± 10
Delay onset symptoms until counterpulsation (h)	$\overline{32}$ (2-144)	$\overline{52}$ (6-192)
Delay onset shock until counterpulsation (h)	$\overline{14}$ (4-72)	$\overline{13}$ (3-96)
Delay onset symptoms until surgery (h)	$\overline{74}$ (33-119)	$\overline{128}$ (35-315)
No. having angiography	18	12
Coronary artery bypass only	7 6 early 1 late	—
Corrective surgery	—	11
Duration of counterpulsation (d)	$\overline{7\cdot 9}$ (1-30)	$\overline{3\cdot 1}$ (1-15)
No. with dialysis	6	5
Hospital survivors	21	4
Late survivors		
Class 1 or 2	2	3
Class 3 or 4	4	0

*Excluding 7 patients whose systemic pressure was unrecordable.
†Measured in 32 patients.

Table 2 *Patients without shock*

No.	26
Male/female	25/1
Age (y)	$\overline{53}$ (37-69)
Previous infarction	8
Site of present infarction	
Transmural anterior	17
Transmural inferior	3
Transmural anterior and inferior	5
Subendocardial	1
Referral from other hospital	13
Heart rate before counterpulsation/min	118 ± 16
Systemic artery pressure before counterpulsation (mmHg)	111/74 (80-180/55-110)
Pulmonary artery pressure before counterpulsation* (mmHg)	32 ± 8
Prognostic index before counterpulsation	
Norris	10·3 ± 1·8
Peel	20 ± 3
Complications of infarction before counterpulsation	
Refractory heart failure	26
Continuing ischaemic pain	12
Conduction disturbance	11
Recurrent ventricular fibrillation or tachycardia	8
Delay in onset of symptoms before counterpulsation (h)	$\overline{84}$ (5-456)
Corrective surgery	1
Coronary artery bypass only	3 early, 1 late
Duration of counterpulsation (d)	7·5 ± 3·7
Hospital survivors	17

*Measured in 18 patients.

Of the 74 patients in shock, 33 died during counterpulsation and another 16 died later in hospital. Of the 49 hospital deaths, 47 were attributable to heart failure (with acute renal failure also present in 32). Two deaths resulted from cardiac tamponade from undiagnosed heart rupture. Mortality rate was highest on the first day of counterpulsation and decreased progressively thereafter

Table 3 *Mechanical complications causing shock*

Septal rupture only	6
Subacute heart rupture with tamponade	3
Septal rupture with subacute heart rupture	2
Papillary muscle rupture	2
Ventricular aneurysm	2
Haemorrhagic pericarditis with tamponade	1
Total	16

(Fig. 1); there was no indication from these mortality figures of secondary deterioration after the first 24 hours of counterpulsation.

Of the 74 patients, 29 underwent cardioangiography during the period of circulatory assistance; 18 underwent cardiac surgery as a consequence. Six had early aortocoronary bypass surgery only, while 11 had correction of a mechanical defect with or without coronary bypass as well (Table 1). Corrective procedures were: closure of septal defect (6), mitral valve replacement (2), excision of aneurysm (1), infarctectomy with pericardial drainage (1), and pericardial drainage alone (1).

Early coronary artery bypass graft surgery did not confer any benefit. Of the 6 patients so treated, 4 died in hospital. Correction of a mechanical defect on the other hand often had dramatic consequences. The 2 patients with haemopericardium treated by open drainage improved greatly though 1 who remained in shock required a further period of counterpulsation after operation before satisfactory renal function returned. Both left hospital in good condition as did the patient whose aneurysm was excised. Neither patient with ruptured papillary muscle and only one with septal defect left hospital; this patient, however, made a complete recovery. The experience with ruptured septum and papillary muscle was disappointing, with only 1 survivor in 10 treated. This may have been because of the late intervention with surgical repair performed 20 to 220 (mean 65) hours after the onset of shock and 8 to 216 (mean 48) hours after initiation of counterpulsation. The mitral valve repair remained intact in both cases undergoing valve replacement, but in 3 of the 6 patients undergoing repair of septal defect (including the survivor) the repair subsequently broke down. The survivor had a further patch inserted 12 weeks after the first operation.

Twenty-five patients left hospital—21 who had no mechanical defect and 4 who did. Sixteen patients died in the follow up period—14 from severe heart failure, 1 from reinfarction, and 1 from cancer. Both patients who underwent early coronary artery bypass grafting alone died in the follow up period. Long-term results were poor (Fig. 2), with only 10 per cent survival at 4 years. Long-term results were dismal in patients without mechanical complications, whose survival rate was 6 per cent at 4 years (there being only 6 of 58 alive at the time of follow up) (Fig. 3). Results were better in patients who underwent correction of a mechanical defect with only 1 late death (from cancer) in 4 hospital survivors. Survivor status was also better in the patients with corrected mechanical defects, all having returned to work or previous activities and all being in New York Heart Association functional class 1 or 2. In contrast, only 2 of the 6 living patients who had no mechanical complication were in functional class 1 or 2.

Late survival and survivor status was related to the delay in initiating counterpulsation after the

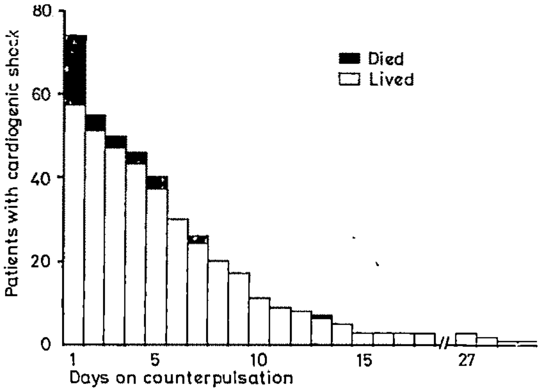

Fig. 1 *Daily mortality during counterpulsation for patients in cardiogenic shock.*

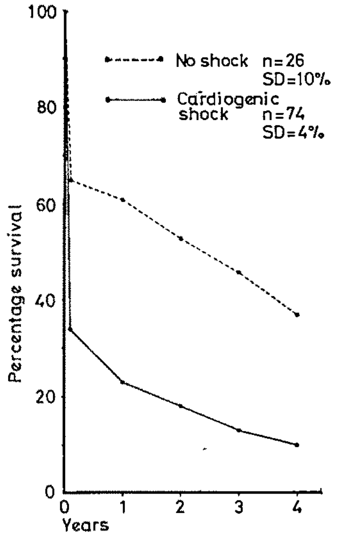

Fig. 2 *Life tables, all patients.*

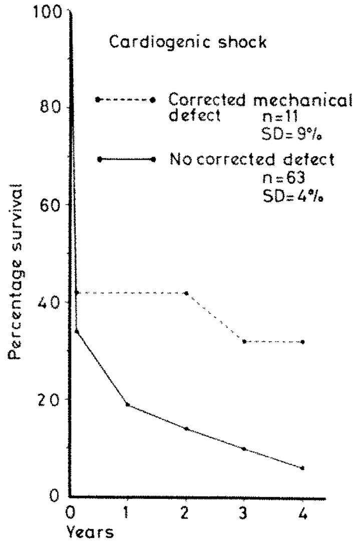

Fig. 3 *Life tables, 74 patients in cardiogenic shock with and without corrected mechanical defects.*

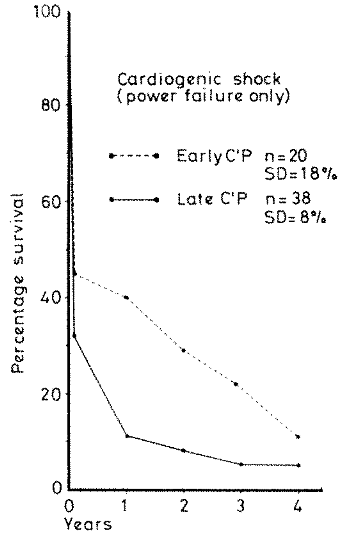

Fig. 4 *Life tables, 58 patients in cardiogenic shock without mechanical defects. Early counterpulsation (CP) which started within 8 hours of the apparent onset of shock; late counterpulsation which started 8 hours after apparent onset of shock.*

onset of shock. For patients without mechanical complications, late survival at 1 to 4 years was almost twice as high in patients undergoing counterpulsation within 8 hours of the apparent onset of shock as compared with those so managed more than 8 hours after the onset of shock (Fig. 4). Both late survivors in functional class 1 or 2 had undergone counterpulsation within 8 hours of the onset of shock, while all 4 late survivors in functional class 3 or 4 had undergone counterpulsation more than 8 hours after onset of shock.

(b) PATIENTS WITHOUT SHOCK (Table 2)

All these patients had severe left ventricular failure, refractory to medical therapy. This was the indication for counterpulsation. All had at least one other complication of infarction in addition—recurrent ischaemic pain (12), conduction disturbances (11), recurrent ventricular fibrillation or tachycardia (8).

All patients showed improvement with initiation of counterpulsation. The most dramatic effect was on ischaemic heart pain which was present in 12 patients; pain was abolished within minutes in 11 patients and within 12 hours in the other. Symptomatic improvement from left ventricular failure was usually manifest within 2 hours, with radiological clearing of pulmonary oedema usually occurring by the third day of counterpulsation. Pulmonary artery pressure fell from 32 ± 8 mmHg before counterpulsation to 19 ± 6 mmHg ($P < 0{\cdot}001$) by the end of the first day, and heart rate from 118 ± 16 beats/minute to 104 ± 17 beats/minute ($P < 0{\cdot}001$) by the end of the first day. Eleven patients had conduction disturbances before counterpulsation; normal conduction was established within 48 hours in 8.

Recurrent ventricular arrhythmias became less frequent with initiation of counterpulsation in the 8 patients so affected. Counterpulsation was continued for 1 to 15 (mean 7·9) days. When counterpulsation was stopped there was little alteration in heart rate or in pulmonary or systemic pressure in the whole group, though in some patients there were signs of deterioration.

Nine patients died in hospital (mortality rate 35%). Six deaths were attributable to heart failure and 3 to primary ventricular fibrillation during hospital convalescence. One patient died during the period of counterpulsation and 8 after this had been terminated. Results were poor in patients treated more than 1 week after the onset of infarction; all but one (with pseudoaneurysm) died in hospital of heart failure. Results were good in patients whose heart failure was associated with continuing ischaemic pain; there was only 1 hospital death in 12 such patients. Four patients underwent coronary artery bypass surgery, 3 in the acute stage and 1 6 weeks after termination of counterpulsation. Of the 3 patients undergoing early coronary artery bypass, 2 died in hospital.

Of the 17 hospital survivors, 5 died during the follow up period. Survival at 4 years was 37 per cent

(Fig. 2). Two late deaths followed reinfarction (1 sudden, 1 from acute cardiac failure) while 3 were attributable to chronic heart failure. Eight of the 12 patients alive at follow up were in functional class 1 or 2 while 4 were in class 3 or 4.

Late results were good in patients with continuing ischaemic pain. There was only 1 late death in this group and 7 of the 10 survivors at follow up were in functional class 1 or 2. The patient with mechanical complication likewise did well: 5 months after discharge he chased and overpowered a burglar.

(c) COMPLICATIONS (Table 4)

Complications of counterpulsation were usually evident early and usually occurred in poor risk patients. Of the 19 complications, 13 occurred on the first day, 4 subsequently during counterpulsation, and 2 after removal of the balloon catheter (Fig. 5); there were no complications after discharge from hospital. Of the 19 complications, 17 occurred in patients with cardiogenic shock, and only 2 in patients without shock. No patient died as a direct result of any complication.

Signs of impaired perfusion of the leg—pallor, coolness, diminished pulses—were often seen without ischaemia after insertion of the balloon catheter into the femoral artery. Such signs were usually transient. Thrombus was frequently found in the femoral artery after removal of the catheter without any signs of ischaemia having been present before. Thrombus was always sought during the removal procedure, and, when present, removed with Fogarty catheters.

Table 4 *Complications of counterpulsation*

Ischaemia of leg (1 with gangrene)	10
Arterial dissection	3
Bleeding (1 with infection)	3
Balloon damage	2
Embolism	1
Total	19

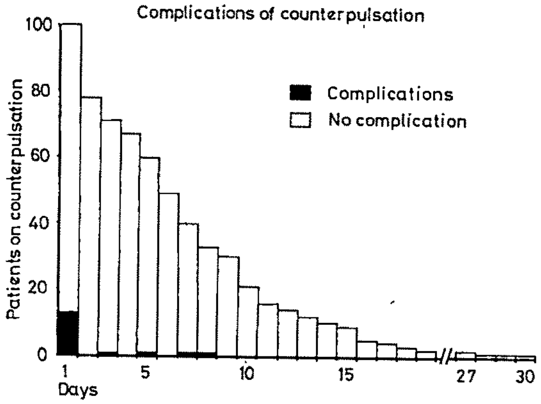

Fig. 5 *Onset of counterpulsation complications in all patients.*

Discussion

Results presented here suggest a wider role for counterpulsation in acute myocardial infarction than currently held. The improved hospital survival for patients with cardiogenic shock is similar to that reported by others who have attributed results to early coronary bypass surgery (Dunkman *et al.*, 1972; Sanders *et al.*, 1972; Leinbach *et al.*, 1973; Miller *et al.*, 1974; Willerson *et al.*, 1975; Bardet *et al.*, 1977; Erich *et al.*, 1977). Our results were no better in patients undergoing bypass surgery than in those treated with counterpulsation alone. These findings were welcome because we had found early angiographic assessment and surgery a complex undertaking, tiring to the patient, logistically difficult, disruptive of routine work, and demoralising to staff when unsuccessful. The findings were not unexpected because we could not understand how bypass surgery performed 48 hours and more after the onset of symptoms could influence the progression of ischaemia to infarction—a process which in most cases appears to be complete within the first 24 to 48 hours of the onset of symptoms (Sobel *et al.*, 1972; Braunwald, 1974; Norris *et al.*, 1975). Proponents of early surgical revascularisation have cited 'balloon dependence' (Dunkman *et al.*, 1972; Sanders *et al.*, 1972) and secondary deterioration on counterpulsation (Dilley *et al.*, 1973; Erich *et al.*, 1977) as reasons for not persevering with counterpulsation alone. We found that patients who were 'balloon dependent' at 1 or 2 days were usually not so at 7 or 14 days. We have rarely seen secondary deterioration during counterpulsation, the usual finding (reflected in haemodynamic patterns and mortality rates (Fig. 1)) being continued improvement with the passage of time. Where reported (Dilley *et al.*, 1973; Erich *et al.*, 1977), secondary deterioration may have been the result of angiographic investigation and trials of weaning. We attributed the gradual improvement with time to gradual recovery of reversibly damaged myocardium (Heyndrickx *et al.*, 1975) and development of collaterals.

Gradual improvement in cardiac performance over several days after infarction has been documented (Russell *et al.*, 1970). It is interesting that the average duration of counterpulsation in this series (7·0 days) was similar to the average duration of vasodilator therapy chosen by Chatterjee *et al.* (1976) (7·6 days) on the basis of stabilisation of haemodynamics and clinical improvement.

Despite the improved early results in patients with cardiogenic shock caused by myocardial power failure the general outlook is still poor with high morbidity and mortality in the ensuing years from chronic cardiac failure. These results have been obtained however in a group of patients who underwent counterpulsation more than 24 hours on average after the onset of symptoms when signs of massive irreparable myocardial damage were already apparent. Results were far better in patients treated early. It is probably unrealistic to expect better results in patients treated as late as those described here.

Results in patients with mechanical defects were similar to those reported elsewhere (Sanders *et al.*, 1972; Leinbach *et al.*, 1973; Bardet *et al.*, 1977). We believe that results would have been even better still had we proceeded expeditiously to counterpulsation, angiography, and surgical correction. Five patients in this series had subacute rupture of the heart (O'Rourke, 1973) with haemopericardium; in 2 cases this was associated with septal rupture. After septal rupture, subacute heart rupture was the most common mechanical complication encountered. Surprisingly there is no mention of this complication in other published series except as a cause of death in patients treated with cardiogenic shock (Kantrowitz *et al.*, 1969; Bardet *et al.*, 1977). Subacute heart rupture proved difficult to diagnose (and was missed completely in 2 patients even at diagnostic angiography), but we believe it should be strongly suspected in patients with late onset of cardiogenic shock (more than 24 hours after onset of symptoms), especially when signs of right heart failure are dominant (O'Rourke, 1973) even in the absence of classical features of tamponade. Our present procedure is to proceed promptly to cardiac surgery in patients with echocardiographic and clinical evidence of tamponade.

Use of counterpulsation in patients with refractory heart failure but without shock was a logical extension of our experience in cardiogenic shock and represented an attempt to prevent shock. After patients with cardiogenic shock, this group has the highest mortality of any occurring after infarction. Surprisingly, only 2 similar series have been reported before (Willerson *et al.*, 1975; Hagemeijer *et al.*, 1977). In the absence of controls it is not possible to be sure how these patients would have fared without counterpulsation. An attempt was made to estimate hospital survival from prognostic indices of Peel *et al.* (1962) and Norris *et al.* (1969). In using these indices it must be conceded that they were developed before the advent of coronary care wards and may overestimate mortality. Against this however coronary care has not led to improved survival in patients with severe heart failure (Meltzer and Kitchell, 1972), and, further, the indices were applied by us to patients after conventional treatment had failed rather than before any treatment had been started. It is, therefore, probable that mortality was reduced by counterpulsation.

As in patients with cardiogenic shock, patients without shock did not benefit from early coronary artery bypass surgery. In addition, results were poor in patients undergoing counterpulsation late after the onset of symptoms (unless a mechanical defect was present) and good in patients treated early especially if there was evidence of continuing ischaemia. These findings are easily explicable on the basis of counterpulsation causing relief of myocardial ischaemia and reduction in infarct size (Mueller *et al.*, 1971; Braunwald, 1974).

After surgical revascularisation, counterpulsation is probably the most powerful method currently known for relieving myocardial ischaemia (Mueller *et al.*, 1971; Braunwald, 1974). Logic dictates that it must have a role in the early stage of acute myocardial infarction. Despite its sound physiological basis and impressive results under experimental circumstances, counterpulsation has been restricted in the main to patients with shock and massive established infarction in whom all conventional treatment has failed. Certainly infarction can spread further in a shocked patient (Page *et al.*, 1971) but it makes little sense to aim at redressing only the secondary effects of shock. The approach to counterpulsation in patients with infarction has been ultraconservative as though the procedure itself carries little chance of benefit and great risk of harm. Chance of benefit indeed appears to be great (provided counterpulsation is initiated early) and the risk of complication quite low. In our hands complications have been infrequent and have posed little risk of life and limb. Contrary to other views (Pace *et al.*, 1976) we believe that the complications are largely those of the insertion procedure in a desperately ill patient. Once counterpulsation is established and the patient responding, the chance of late complication is remote and very low indeed when judged against the chance of clinical improvement. Risk of late complications we believe should not dictate early termination of counterpulsation within 1 to 2 weeks in a patient who is responding well.

There has been increasing use of counterpulsation in coronary insufficiency or threatening infarction (Mundth, 1976). That counterpulsation has established a role in this low risk condition testifies to the safety of the procedure itself.

We have sought no experience in this area, being currently satisfied with conventional treatment: over the past 5 years we have had 7·9 per cent infarction rate with 5·1 per cent mortality rate in 79 patients with coronary insufficiency, refractory to medical therapy, who underwent aortocoronary bypass surgery. Happy as we are with the relative safety of counterpulsation in poor risk patients, we have reservations about the risk against possible benefit in patients with coronary insufficiency.

To date clinical experience with counterpulsation in myocardial infarction has been confined almost exclusively to 2 extremes of the clinical spectrum—from threatening infarction on the one hand to cardiogenic shock on the other: from a condition with around 5 per cent mortality risk on conventional treatment on the one hand to 95 per cent on the other Evidence of clinical benefit in the two groups of patients suggests a role throughout the spectrum. The data presented in this paper support such a concept: that counterpulsation may have an important place by itself in treatment of acute infarction, provided intervention is prompt. We are currently investigating this with a randomised controlled trial.

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Comparative haemodynamic and peripheral vasodilator effects of oral and chewable isosorbide dinitrate in patients with refractory congestive cardiac failure[1]

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SUMMARY The effects of oral (30 mg) and chewable (10 mg) isosorbide dinitrate on haemodynamics, venous capacitance, and calf blood flow were compared in a double-blind trial in 18 patients with refractory chronic congestive heart failure with pulmonary artery end-diastolic pressures $\geqslant$18 mmHg. Cardiac output and right heart pressures were measured with a Swan-Ganz thermodilution catheter, arterial pressure through an indwelling radial artery cannula, and venous capacitance and calf blood flow by vascular occlusion plethysmography. Both agents reduced pulmonary artery end-diastolic pressures $>$10 per cent in 15 patients ('responders') but by $\leqslant$10 per cent in 3 others ('non-responders'). In the responders, both agents produced significant decreases in mean arterial pressure, in pulmonary artery end-diastolic pressures, and in mean right atrial pressure. Oral (but not chewable) isosorbide dinitrate produced a significant increase in cardiac index and stroke volume index while decreasing systemic vascular resistance and heart rate. Both agents increased venous capacitance significantly but without a comparable effect on calf blood flow. The onset of action for both agents was apparent within 10 minutes; the peak effect, however, occurred significantly earlier for the chewable isosorbide dinitrate, whereas the duration of action was longer for oral isosorbide dinitrate. The overall data thus indicate that both oral and chewable isosorbide dinitrate may have significant effects on vascular capacitance bed but because of its more pronounced effect on ventricular function and its more prolonged duration of action, oral isosorbide dinitrate appears to be the preferred agent for protracted oral treatment in congestive cardiac failure.

The effects of peripheral vasodilators upon cardiac haemodynamics have been studied extensively since the recognition of their efficacy in patients with heart failure secondary to acute myocardial infarction in the early 1970's (Majid *et al.*, 1971; Franciosa *et al.*, 1972; Gold *et al.*, 1972; Chatterjee *et al.*, 1973; Cohn, 1973). After the initial documentation of the profound haemodynamic effects of intravenous vasodilators, attention has focused recently on the use of oral and sublingual preparations (Franciosa *et al.*, 1974; Gray *et al.*, 1975; Mikulic *et al.*, 1975; Chatterjee *et al.*, 1976; Kovick *et al.*, 1976; Mantle *et al.*, 1976; Williams *et al.*, 1977) as potential agents for the long-term management of cardiac failure, particularly in patients having satisfactory responses to intravenous agents in acute studies. Most prominent of this class of agents are hydralazine (Chatterjee *et al.*, 1976) and nitrates (Franciosa *et al.*, 1974; Gray *et al.*, 1975; Mikulic *et al.*, 1975; Kovick *et al.*, 1976; Mantle *et al.*, 1976; Williams *et al.*, 1977). Though both these regimens have been found to improve symptoms as well as cardiac haemodynamics (Franciosa *et al.*, 1974; Gray *et al.*, 1975; Mikulic *et al.*, 1975; Williams *et al.*, 1977) in congestive heart failure, no adequately controlled clinical studies in which the time of onset, duration of effect, haemodynamic potency, and mechanism of action of different

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preparations of vasodilators were compared in the same individual have so far been reported. The present study has, therefore, served to compare and define those important clinical variables with two of the potentially most useful agents, oral and chewable isosorbide dinitrate. Our results not only confirm and extend the results of the previous haemodynamic studies for these agents, but also indicate that substantial differences between them exist while providing an insight into the potential mechanism for the lack of expected haemodynamic responses found in the non-responders.

Patient selection and methods

The study was undertaken with 18 patients, 17 men and 1 woman (mean age 67 years, range 21 to 82 years) who had congestive heart failure (functional class III-IV, New York Heart Association classification) as judged by clinical as well as radiological criteria. All patients considered refractory to conventional therapy consisting of adequate doses of digitalis and diuretics had been on bed rest for at least 3 days before entry into the study. Diuretics were discontinued at least 12 hours before the study. Only those patients who had a pulmonary artery diastolic pressure (PADP) or capillary wedge pressure (PCP) $\geqslant 18$ mmHg (see below) were included in the study.

The cause of heart failure was attributed to coronary artery disease in 12 patients, hypertensive heart disease in 1, peripartum cardiomyopathy in 1, alcoholic cardiomyopathy in another, and idiopathic cardiomyopathy in the remaining 3. Physical findings, with or without the presence of significant 'V' waves in the wedge pressure tracings, consistent with mitral regurgitation were encountered in 6 patients. There were no other valve lesions. Acute myocardial infarction was excluded in each instance by the conventional electrocardiographic and serum enzyme criteria. Three of the 18 patients had been previously treated with sublingual isosorbide dinitrate.

Intra-arterial pressure (AP) was measured through a 19 gauge, 2-inch indwelling catheter inserted percutaneously into the radial artery. Pulmonary artery (PA), pulmonary capillary (PC), and right atrial (RAP) pressures were measured through a no. 7 Fr Swan-Ganz thermodilution catheter placed via an antecubital vein through a cut-down, or percutaneously through the internal jugular vein. Cardiac output (CO) was measured in triplicate by the thermodilution technique (Ganz and Swan, 1972).

In 12 patients, venous capacitance (VC) and calf blood flow (CBF) were measured. Venous capacitance was measured in one of the lower extremities by the equilibrium method using a pneumatic plethysmograph (Vyden *et al.*, 1974), with a venous occluding pressure of 30 mmHg. Calf blood flow was also measured by plethysmography with a distal occlusive pressure of 200 mmHg.

Derived haemodynamic indices were calculated from the measured variables as follows: cardiac index (CI) = CO/body surface area (l/min per m^2); stroke volume index (SI) = stroke volume (SV)/body surface area (ml/m^2 per beat); systemic vascular resistance (SVR) = $80 \times (\overline{AP}\text{-}\overline{RAP})$ CO (l/min) (dynes s^{-1} cm^{-5}); stroke work index (SWI) = $(\overline{AP}\text{-}\overline{PCP}$ or PADP$) \times SI \times 0{\cdot}0136$ (g/m^2 per beat); and pulmonary vascular resistance (PVR) = $80 \times (\overline{PA}\text{-}\overline{PCP}$ mmHg)/CO l/min (dynes s^{-1} cm^{-5}).

DESIGN OF STUDY

Baseline measurements were obtained every 30 minutes for a minimum of one hour. They were considered stable only when pulmonary artery

Table *Peak and duration of action of chewable (10 mg) and oral (30 mg) isosorbide dinitrate in patients (n = 15) with congestive heart failure*

Patient		*Time* *(min)*	*HR* *(b/min)*	$\overline{AP}$ *(mmHg)*	*PASP/PADP* *(mmHg)*	$\overline{RAP}$ *(mmHg)*
Chewable isosorbide dinitrate						
	Control	0	83·6 ± 1·6	87·8 ± 4·3	56·7 ± 4·2/29·2 ± 1·9	10·9 ± 1
Mean ± SEM	Peak	27·0 ± 4·4	82·9 ± 2·1	79·6 ± 2·9*	39·5 ± 4·0/*18·9 ± 1·6*	7·7 ±
	Final	136 ± 12·4	82·2 ± 2·1	84·9 ± 3·0	51·9 ± 4·8/27·2 ± 2·2§	11·0 ± 1
Oral isosorbide dinitrate						
	Control	0	85·3 ± 3·4	88·3 ± 3·1	57·1 ± 4·8/29·5 ± 2·5	13·4 ±
Mean ± SEM	Peak	69 ± 14·6	80·1 ± 3·6§	78·2 ± 2·3*	41·3 ± 4·8/*19·1 ± 2·1*	8·8 ± 1
	Final	212 ± 9·9	79·2 ± 3·4‡	83·5 ± 2·7¶	50·1 ± 4·4/¶24·3 ± 1·9*	10·7 ± 1

*P < 0·001; †P ≤ 0·005; ‡P < 0·01; §P < 0·02; ¶ < 0·05.

HR, heart rate; $\overline{AP}$, mean arterial blood pressure; PASP, pulmonary artery systolic pressure; PADP, pulmonary artery diastolic pressure; $\overline{RAP}$, right atrial pressure; CI, cardiac index; SI, stroke volume index; SWI, stroke work index; SVR, systemic vascular resistance; PVR, pulmonary v
resistance; VC, venous capacitance.

diastolic pressure or pulmonary capillary pressure and vital capacity were within 10 per cent in 2 consecutive measurements. As soon as the stable baseline was reached, either chewable isosorbide dinitrate, 10 mg, or oral isosorbide dinitrate, 30 mg, was administered. For a chewable compound, the patient was instructed to chew the tablet under supervision of a physician for a minimum of 2 minutes. For the oral compound, the patient was instructed to swallow the tablets. In order to establish a double-blind format, each time the patient had to swallow 3 tablets (30 mg oral isosorbide dinitrate or placebo) and to chew one tablet (placebo or 10 mg chewable isosorbide dinitrate). Subsequently, measurements of all variables were taken at 15-minute intervals for the first hour and every 30 minutes thereafter for a minimum of 2 hours and a maximum of 4 hours until the value of PADP had returned within 10 per cent of control level. Thereafter, the same procedure was repeated for the second drug. If the pulmonary artery diastolic pressure had not returned to a value ⩾18 mmHg after the first agent, the study with the second drug was delayed until this value was achieved.

The dose of chewable or oral isosorbide dinitrate used in the study was chosen to produce haemodynamic effects of a comparable magnitude as indicated in previous reports (Franciosa *et al.*, 1974; Mikulic *et al.*, 1975). Statistical analyses were carried out by the use of Student's t tests for paired and unpaired data.

Results

Patients in whom pulmonary artery diastolic pressure had decreased by more than 10 per cent relative to their control values were designated as responders, whereas those who failed to respond to oral isosorbide dinitrate (3 patients) and/or to chewable isosorbide dinitrate (3 patients) were designated as non-responders.

RESPONDERS: TIME OF ONSET, PEAK EFFECT, AND DURATION OF ACTION

There were no significant differences between the two sets of control values though the baseline cardiac index and systemic vascular resistance for the oral isosorbide dinitrate were somewhat lower and higher, respectively, than those for the chewable isosorbide dinitrate (Table). The onset of action of the haemodynamic changes was usually apparent during the first 15 minutes for both drugs, the effects with chewable isosorbide dinitrate being noticeable earlier than those after oral isosorbide dinitrate which frequently occurred within the first 7 minutes of drug ingestion.

The differences between the effects of oral and chewable isosorbide dinitrate with respect to measured and derived haemodynamic variables are presented in the Table and Fig. 1-3. The peak haemodynamic effects occurred significantly earlier with chewable isosorbide dinitrate (27 vs. 69 min, $P < 0{\cdot}01$). Compared with the control values, the peak changes were statistically significant and of comparable magnitude for both oral and chewable isosorbide dinitrate with respect to intra-arterial pressure: 11·4 per cent vs. 9·3 per cent (Fig. 1); right atrial pressure: 34·3 per cent vs. 29·4 per cent (Fig. 2); pulmonary artery systolic pressure: 27·7 per cent vs. 30·3 per cent; pulmonary artery diastolic pressure: 35·3 per cent vs. 35·3 per cent (Fig. 2); pulmonary vascular resistance: 37·8 per cent vs. 33·5 per cent, respectively. Both agents also increased stroke work index. However, only the oral isosorbide dinitrate produced a significant increase in cardiac index (14·8%) and stroke index (19·6%; Fig. 3), more significant improvement in left ventricular function (Fig. 4). Only isosorbide dinitrate also produced a decrease in systemic

min per m^2)	*SI* (*ml/b per* m^2)	*SWI* (*g m/b per* m^2)	*SVR* *dynes* s^{-1} cm^{-5}	*PVR* *dynes* s^{-1} cm^{-5}	*VC* *ml/100 ml*
6 ± 0·16	24·9 ± 2·1	19·5 ± 2·8	1612 ± 90	266 ± 36	0·53 ± 0·42
2 ± 0·11	25·9 ± 1·5	21·8 ± 2·2¶	1515 ± 71	177 ± 26*	0·68 ± 0·54¶
4 ± 0·16	24·1 ± 2·2	19·5 ± 2·4	1721 ± 141	289 ± 64	0·51 ± 0·14
3 ± 0·12	22·5 ± 1·9	18·3 ± 2·0	1819 ± 122	323 ± 54	0·42 ± 0·33
0 ± 0·12¶	26·9 ± 2·0‡	21·7 ± 1·9§	1542 ± 86†	201 ± 36†	0·73 ± 0·66¶
6 ± 0·10	25·7 ± 1·8¶	21·1 ± 2·2¶	1782 ± 113	271 ± 48	0·58 ± 0·19

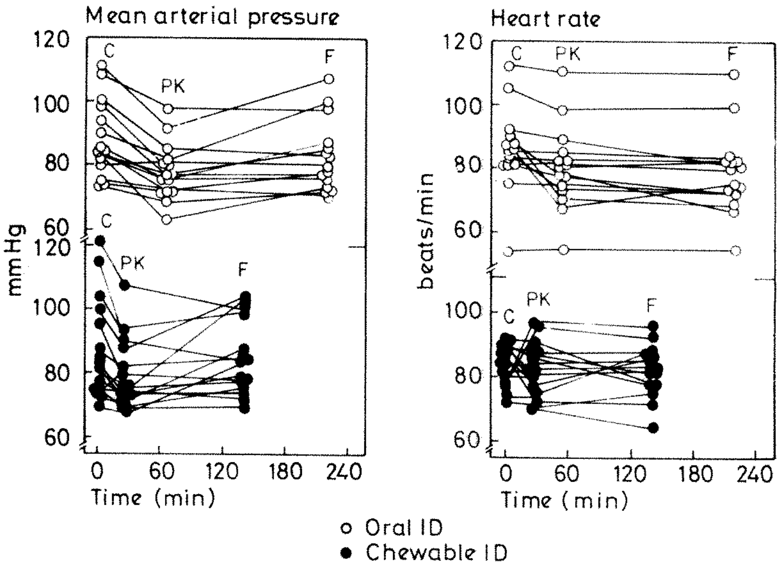

Fig. 1 *Effects of oral and chewable isosorbide dinitrate (ID) on mean arterial pressure and heart rate. Note that the peak (PK) effects are earlier with the chewable preparation than with the oral. F = final set of values after each drug intervention.*

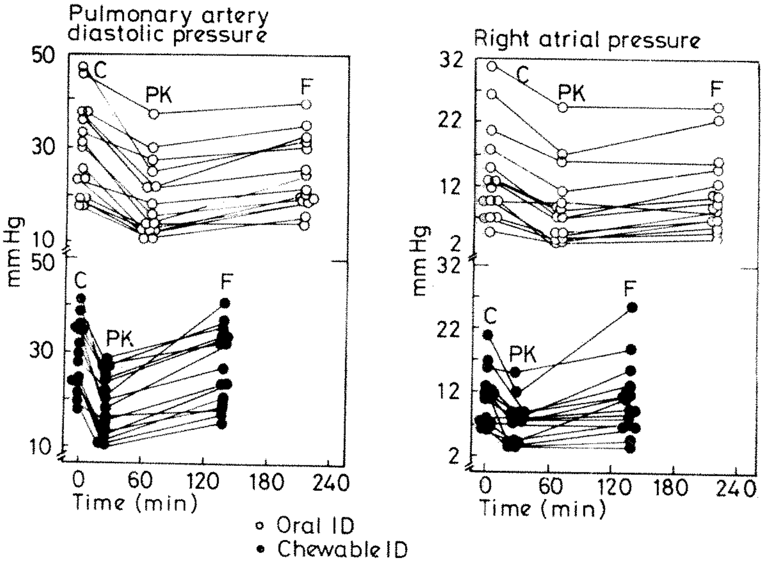

Fig. 2 *Changes in pulmonary artery diastolic pressure and right atrial pressure after oral and chewable ID. See text for comments.*

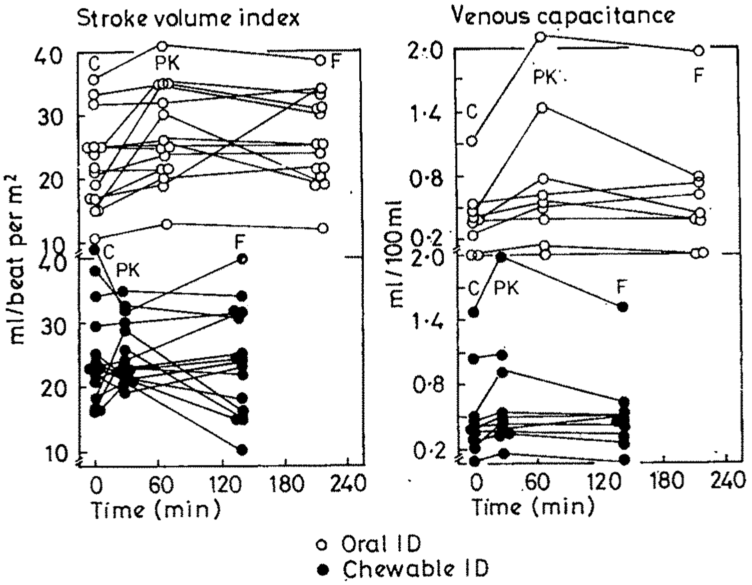

Fig. 3 *Changes in stroke volume index and in venous capacitance after oral and chewable ID. See legend for Fig. 1 for the meaning of abbreviations, and the text for discussion.*

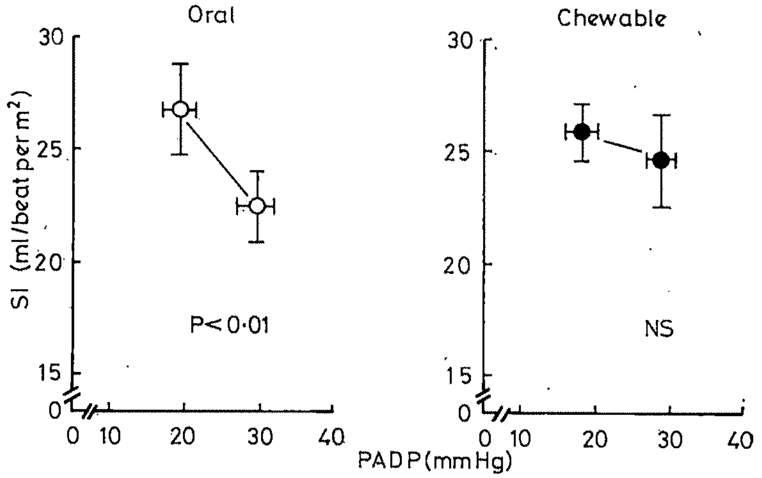

Fig. 4 *Improvement in left ventricular function in 15 patients with refractory congestive heart failure as shown by a significant increase in stroke volume index (SI) and concurrent reduction in left ventricular filling pressure, expressed by pulmonary artery diastolic pressure, was only achieved with oral ID (30 mg) (left panel). Chewable ID (10 mg) (right panel) had no significant effect upon SI.*

vascular resistance (15·2%) and heart rate (6·1%) (Fig. 1). Venous capacitance was significantly increased by both agents, the changes tending to be more pronounced with oral isosorbide dinitrate (75% vs. 29%; Fig. 3) though the differences between the chewable isosorbide dinitrate and oral isosorbide dinitrate did not reach a level of statistical significance. Changes in calf blood flow were variable and insignificant with both preparations.

The duration of action was significantly longer

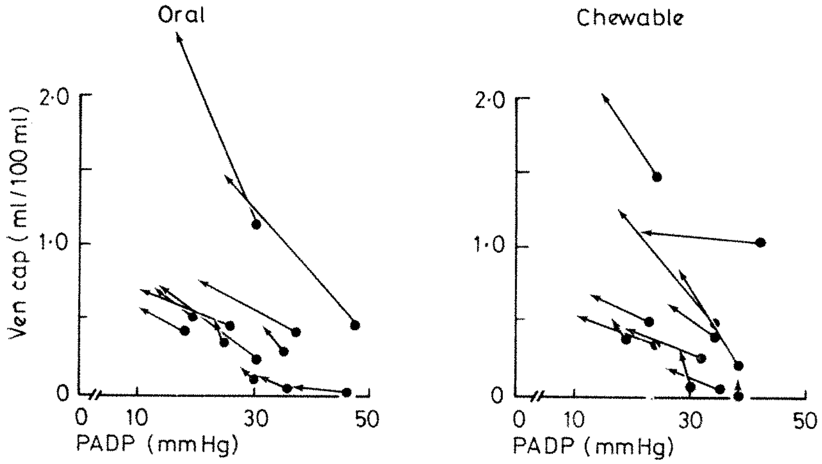

Fig. 5 *The effects of 30 mg of oral ID (left panel) and 10 mg of chewable ID (right panel) on venous capacitance and pulmonary artery diastolic pressure (PADP) in 12 patients with refractory congestive heart failure are illustrated in this figure. The magnitude of the effect of these two agents on these two indices was very similar. The graph shows that those patients with very decreased venous capacitance had a tendency to have the smallest changes in both PADP and venous capacitance.*

for oral isosorbide dinitrate (212 vs. 136 min, $P < 0{\cdot}001$; Table). In addition, in 9 of the 15 patients given oral isosorbide dinitrate, pulmonary artery diastolic pressure had not returned to within 10 per cent of the control values after 4 hours, whereas this occurred with only 4 patients given chewable isosorbide dinitrate.

NON-RESPONDERS

Even though the pulmonary artery diastolic pressure did not decrease more than 10 per cent in all patients in this group, they exhibited a uniform though small decrease in pulmonary vascular resistance. In 4, this was attributed to a moderate increase in cardiac output and in 2, to a moderate decrease in mean pulmonary artery pressure. Only 1 patient failed to respond to both agents. There were no common haemodynamic or clinical features among these patients, except for their tendency to have a substantially lower venous capacitance compared to the responders. As illustrated in Fig. 5, patients who had the lowest initial venous capacitance had a tendency to exhibit the smallest change in both venous capacitance and pulmonary artery diastolic pressure after isosorbide dinitrate.

Discussion

The data from our double-blind comparative haemodynamic studies with oral and chewable isosorbide dinitrate in the same patients have indicated that both agents can produce sustained and comparable reductions in the pulmonary capillary wedge pressure, the main determinant of pulmonary congestion; these findings agree with previous observations (Franciosa *et al.*, 1974; Mikulic *et al.*, 1975; Bussmann *et al.*, 1977; Williams *et al.*, 1977). However, in the present study an important difference in the effects between oral and chewable isosorbide was found with respect to changes in stroke volume index and systemic vascular resistance. Administration of oral isosorbide resulted in a 20 per cent increase in stroke volume index and a 15 per cent decrease in systemic vascular resistance whereas the effect of chewable isosorbide was negligible. Williams *et al.* (1977) who noted a consistent decrease in left ventricular filling pressure using oral isosorbide failed to document significant increases in stroke volume index or decreases in systemic vascular resistance, except in patients whose pulmonary capillary pressure had not fallen to levels below 12 mmHg after drug administration. Even though the oral dose used in the present study was larger than that (20 mg) given by Williams and his colleagues, the effect on the left ventricular filling pressure was comparable. The differences between the two sets of data suggest that the type of response observed may be dose-dependent, and that a larger dose of oral isosorbide dinitrate may induce a more consistent afterload reduction and consequent functional improvement. Franciosa *et al.* (1974) also reported a decrease in left ventricular filling pressure after oral isosorbide dinitrate, though the observed change in their study was smaller than that in ours (25% vs. 35%). Systemic vascular resistance and other flow-dependent variables were not measured in their study. Bussmann *et al.* (1977), treating patients with left ventricular failure secondary to an acute myocardial infarction, found a similar fall in left ventricular filling pressure using the same total dose of oral isosorbide dinitrate (30 mg), though it was administered in two doses (10 and 20 mg) at 30-minute intervals. The major haemodynamic changes were apparent after the initial dose (10 mg). In their study the criterion for left ventricular failure was a left ventricular filling pressure greater than 20 mmHg, and it was only among this group that a fall in left ventricular filling pressure was associated with an increase in cardiac output.

A significant decrease in heart rate after oral but not chewable isosorbide dinitrate, observed in our study as well as in those of others in patients with congestive heart failure using nitroprusside (Franciosa *et al.*, 1972) or glyceryl trinitrate (Gold *et al.*, 1972), is of particular interest. The decline in heart rate which occurred despite a fall in blood pressure has not been a consistent finding, however, in patients without heart failure (Kasparian *et al.*, 1975; Bussmann *et al.*, 1977).

In the only previous study on the haemodynamic effects of chewable isosorbide dinitrate in patients with congestive heart failure which did not include flow-related measurements, Mikulic *et al.* (1975) found a similar fall in left ventricular filling pressure but they did not find a significant change in arterial pressure. This difference was probably related to the much lower resting blood pressure in their patient population (106/78 vs. 133/66).

The differences in the response in stroke index and systemic vascular resistance induced by the two agents further illustrate the difficulties inherent in the interpretation of data from comparative drug studies in man. Usually such studies are conducted using drugs of differing chemical structures, and dissimilar responses are often attributed to differences in the intrinsic pharmacological properties of the agents themselves. Our study shows that substantial differences in response may be obtained in the same patient with the same drug at approximately comparable doses, when the mode of administration is altered. Whether this difference is in fact related to the route of drug administration cannot, however, be ascertained from the results of the present study.

In addition to the differences in the effects on stroke volume and systemic vascular resistance, the two agents were found to be substantially different in the peak effect and overall duration of action. The onset of action of chewable isosorbide was invariably apparent within 10 minutes of drug administration with a peak activity being attained by 27 minutes, thus making it a very suitable compound for acute administration in patients in hospital. Since its mean duration of action is only 136 minutes, which is very similar to that reported for sublingual isosorbide dinitrate (Gray *et al.*, 1975; Kovick *et al.*, 1976), it is obviously of limited value for long-term treatment of congestive cardiac failure. In contrast, oral isosorbide had a similar onset of action, starting within 15 to 20 minutes but reaching peak activity in 69 minutes with its effect being sustained for at least 3½ hours; these characteristics of the drug, as have also been noted by previous investigators (Franciosa *et al.*, 1974; Williams *et al.*, 1977), greatly enhance clinical usefulness for long-term treatment.

Our measurements of peripheral vascular functions undertaken in association with the haemodynamic studies in 12 of the 18 patients suggest that both agents might exert their major effect by peripheral venodilatations. In 6 of 9 responders to oral isosorbide dinitrate and in 6 of the 10 responders to chewable isosorbide dinitrate, venous capacitance was near normal before drug administration; it increased significantly after both oral and chewable isosorbide dinitrate. The mean increases in venous capacitance tended to parallel the decreases in left ventricular filling pressure. In contrast, venous capacitance was abnormally low in all the patients who exhibited little or no response to drug administration. The arterial flow to the lower limbs showed little change in both responders as well as non-responders to the drugs. It is of course possible that additional specific vascular beds may also be particularly responsive to the vasodilator action of isosorbide. The dramatic fall in pulmonary vascular resistance and the fall in pulmonary artery systolic pressure, often occurring even in the absence of changes in left ventricular filling pressure, may suggest a direct vasodilator effect of the nitrate on the pulmonary vasculature as has been found with glyceryl trinitrate (Ferrer *et al.*, 1966). Furthermore, the increase in cardiac index and stroke index induced by oral isosorbide, despite a consistent decline in arterial pressure, is suggestive of a concomitant element of afterload reduction (Cohn, 1973).

Although limited, these data suggest that the failure of chewable as well as oral isosorbide to induce the expected response in the presence of severe heart failure in certain patients may be related to the status of venous capacitance at the time of drug administration; if such were the case, these studies may be helpful in selecting patients who might derive benefit from protracted vasodilator therapy in recalcitrant congestive cardiac failure. The data have indicated that in a substantial number of patients, isosorbide dinitrate may produce a beneficial effect on haemodynamic functions lending further support for the use of peripheral vasodilators in the treatment of severe congestive cardiac failure. Though both the chewable and the oral preparation are both effective in reducing pulmonary capillary pressure in cardiac decompensation, oral isosorbide appears to have substantial advantages for outpatient use, especially in relation to its prolonged duration of action.

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Study of left ventricular pressure-volume relations during nitroprusside infusion in human subjects without coronary artery disease[1]

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SUMMARY Studies were made on 21 patients, 8 without any symptoms of left ventricular failure, group 1, and 13 with clinical symptoms of heart failure, group 2. Cardiac output, mean aortic and left ventricular pressures (using catheter tip micromanometer), and ventricular volume (obtained from left ventricular cineangiograms) were measured before and during nitroprusside infusion. The heart rate did not change in either of the groups. Only in group 2 did cardiac index and stroke volume increase significantly. Mean aortic pressure and total systemic vascular resistance decreased significantly in both the groups. Left ventricular end-diastolic pressure decreased significantly in both the groups, but this decrease was greater in group 2 (9 mmHg compared with 3 mmHg for group 1). The decrease in the left ventricular end-diastolic volume was similar in both the groups. The decrease in left ventricular end-systolic pressure was greater in group 1, but the decrease in the left ventricular end-systolic volume was greater in group 2.

These facts are explained by the differences in the active and passive left ventricular pressure-volume relations in the two groups.

Many reports (Franciosa *et al.*, 1972; Chatterjee *et al.*, 1973; Miller *et al.*, 1975; Rossen *et al.*, 1976) have shown that vasodilator therapy is effective in acute and chronic left ventricular failure. Though it leads consistently to a decrease in aortic pressure, systemic vascular resistance, and left ventricular filling pressure, the changes in cardiac output have been less uniform.

The purpose of this study was to analyse the left ventricular pressure-volume diagram before and during nitroprusside infusion and to elucidate the effects of nitroprusside on cardiac output.

Subjects and methods

After obtaining informed consent, the haemodynamic and the angiographic changes before and during nitroprusside infusion were studied in 21 patients. These were 16 men and 5 women (the age range was from 23 to 63 years). All the patients were in regular sinus rhythm. None had valvular heart disease, septal defects, or left bundle-branch block, nor were there any clinical or electrocardiographic signs of coronary artery disease.

The patients were grouped in two categories. Group 1 comprised 8 patients who had never had symptoms of heart failure. Four had a primary hyperkinetic heart syndrome (Guazzi *et al.*, 1975). Group 2 consisted of 13 patients all of whom were in cardiac failure. Some were on diuretic therapy, but no patient was taking digitalis. All had idiopathic cardiomyopathy.

The haemodynamic data recorded before and during nitroprusside therapy were as follows. (1) Cardiac output (CO = l/min) measured by the indocyanine green dilution technique: the dye was injected into the right atrium and sampled in the main pulmonary artery through a 7 F Swan-Ganz catheter. Cardiac index (CI) and stroke volume (SV) were calculated as follows:

$CI = \frac{CO}{BSA}$ (l/min per m^2), where BSA is body surface area. $SV = \frac{CO}{HR}$ (ml) where HR is heart rate.

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Table *Haemodynamic data before (C) and during (N) nitroprusside infusion*

	HR/ min		*CI (l/min per m²)*		*SV dye (ml)*		*SVA (ml)*		$\overline{MAP}$ *(mmHg)*		*TSVR dyne* s^{-1} cm^{-5}		*LVEDP (mmHg)*	
	C	*N*	*C*	*N*	*C*	*N*	*C*	*N*	*C*	*N*	*C*	*N*	*C*	*N*
Group 1														
1	100	92	4·8	4·5	68	68	69	71	160	120	1882	1523	8	4
2	80	80	3·7	4·1	76	82	77	84	100	84	1311	1018	8	6
3	65	70	2·8	3·1	69	65	62	62	86	65	1528	1040	8	3
4	70	65	3·3	3·5	85	86	91	82	88	60	1315	858	6	4
5	75	95	3·8	4·3	100	90	105	72	93	78	992	734	6	3
6	110	120	6·0	6·0	72	67	60	56	90	80	900	790	6	4
7	70	80	4·0	3·5	93	71	73	63	100	70	1240	982	4	1
8	60	70	4·2	3·7	140	104	155	84	80	70	766	767	10	4
Mean	78	84	4·1	4·1	88	79	86	72	100	78	1241	964	7	4
±	±	±	±	±	±	±	±	±	±	±	±	±	±	±
SE	17	17	0·9	0·9	24	14	31	11	25	18	360	255	2	1·4
P value	NS		NS		NS		NS		P < 0·01		P < 0·01		P < 0·001	
Group 2														
9	115	110	2·2	3·1	34	50	22	47	90	84	1800	1221	30	22
10	90	90	1·7	2·0	31	37	50	50	80	68	2245	1600	10	6
11	70	68	2·6	2·6	65	67	54	53	80	64	1406	1120	20	6
12	90	90	1·9	1·7	36	36	50	40	108	76	2468	1842	18	8
13	84	82	2·2	2·5	48	57	40	40	65	50	1238	851	30	12
14	110	100	2·0	4·2	34	77	42	75	64	54	1365	561	32	20
15	61	70	2·8	2·9	67	60	52	53	70	58	1400	1325	4	2
16	90	85	2·8	2·5	66	63	73	62	84	60	1120	980	10	3
17	70	75	1·7	2·8	51	68	45	85	86	64	1911	994	10	4
18	92	100	1·6	1·6	39	39	40	47	76	70	1688	1435	16	8
19	90	95	2·2	2·4	34	36	28	40	88	74	2270	1741	10	4
20	110	105	1·3	2·5	21	43	27	77	68	55	3820	2985	26	12
21	100	100	2·6	2·9	49	56	43	59	100	88	1632	1530	8	2
Mean	90	90	2·1	2·6	44	53	43	56	81	67	1874	1399	17	8
±	±	±	±	±	±	±	±	±	±	±	±	±	±	±
SE	16	13	0·5	0·7	15	13	13	15	13	11	719	601	10	7
P value	NS		P < 0·05		P < 0·05		P < 0·05		P < 0·001		P < 0·01		P < 0·001	

HR, heart rate; CI, cardiac index; SV dye, stroke volume derived from dye dilution technique; SVA, angiographic stroke volume; $\overline{\text{MAP}}$, mean pressure; TSVR, total systemic vascular resistance; LVEDP, left ventricular end-diastolic pressure; LVEDV, left ventricular end-diastolic ve LVESV, left ventricular end-systolic volume; EF, ejection fraction; LVESP, left ventricular end-systolic pressure; SE, standard error; NS, n nificant; NP, nitroprusside.

(2) Left ventricular and ascending aortic pressures (mmHg) were recorded using a catheter tip micromanometer (Millar 5 F). (3) The left ventricular cineangiograms were performed in the frontal plane (50 frames/s). Left ventricular volumes were calculated using the area length method of Dodge *et al.* (1966) and a grid calibration technique. The first 3 to 5 beats after injection of contrast were used for volume calculations. The post-ectopic beats were excluded.

Aortic pressure was recorded at a paper speed of 500 mm/s during the angiogram, using a micromanometer placed in the ascending aorta. A single unit manually controlled marker permitted simultaneous synchronised measurements of angiographic films and pressure tracings from the beginning of the injection phase. It was possible to obtain the following indices before and during vasodilator infusion. (1) The systolic portion of the left ventricular pressure volume relation. The left ventricular systolic pressure was accepted as identical to the aortic systolic pressure. (2) The variations in the instantaneous pressure-volume relation with time. Intervals were measured from the peak of the R wave of the electrocardiogram.

The end-diastolic point of the ventricular pressure-volume diagram was established from the angiographic end-diastolic volume and from the end-diastolic ventricular pressure (LVEDP) obtained immediately before angiography. In this pressure-volume diagram, the end-diastolic volume is the largest volume and the end-systolic volume (ESV) is the smallest volume. The end-systolic pressure (ESP) is the pressure related to end-systolic volume and not to the dicrotic notch.

We then calculated (a) total systemic vascular resistance thus:

$$\text{TSVR} = \frac{\overline{\text{MAP}} \times 80}{\text{CO}} (\text{dyne s}^{-1}\,\text{cm}^{-5}),$$

where $\overline{\text{MAP}}$ is mean aortic pressure mmHg, and CO is cardiac output l/min, and (b) the left ventricular ejection fraction as:

LVEDV (*ml*)		*LVESV* (*ml*)		*EF* (%)		*LVESP* (*mmHg*)		$\frac{LVESP}{LVESV}$ (*mmHg/ml*)		*Maximum value of* $\frac{LVESP}{LVESV}$		*Rate of NP administration* (μg/min)
C	*N*	*C*	*N*	*C*	*N*	*C*	*N*	*C*	*N*	*C*	*N*	
130	117	61	46	53	60	185	140	3·0	3·0			15
142	126	65	42	54	66	132	90	2·0	2·1			25
108	95	46	33	57	65	95	75	2·1	2·3			40
111	90	20	12	82	86	106	62	5·3	5·2			40
138	95	33	23	76	75	108	70	3·3	3·0			30
74	68	14	12	82	80	108	90	7·7	7·5			60
110	91	37	28	66	70	116	80	3·1	2·9			20
205	120	50	36	70	70	100	78	2·0	2·2			35
127	100	41	29	67	72	119	86	3·6	3·5			
± 38	± 19	± 18	± 13	± 12	± 10	± 29	± 24	± 1·9	± 1·9			
P < 0·05		P < 0·01		NS		P < 0·001		NS				
265	260	243	212	10	16	85	70	0·3	0·3	0·4	0·4	60
260	237	210	187	19	22	80	60	0·4	0·3	0·4	0·4	35
231	209	177	156	23	25	90	80	0·5	0·5			40
207	170	157	130	20	21	110	86	0·7	0·7			40
162	145	122	105	24	27	74	58	0·6	0·6			20
310	300	268	224	13	25	64	48	0·2	0·2	0·3	0·3	30
150	130	98	77	34	40	82	64	0·8	0·8			50
210	172	137	110	35	36	94	72	0·7	0·7			20
400	300	355	215	11	28	90	50	0·2	0·2	0·3	0·3	50
305	280	266	233	12	18	90	70	0·3	0·3	0·4	0·4	60
210	200	182	160	13	20	104	84	0·6	0·5	0·7	0·6	30
330	300	302	223	10	25	64	42	0·2	0·2			25
130	125	82	66	36	47	104	90	1·3	1·4			40
244	218	200	161	20	27	87	67	0·5	0·5			
± 78	± 66	± 83	± 59	± 9	± 9	± 15	± 15	± 0·3	± 0·3			
P < 0·01		P < 0·01		P < 0·01		P < 0·01		NS				

$$EF\% = \frac{SV}{LVEDV} \times 100,$$ where SV is angiographic stroke volume (ml) and LVEDV is left ventricular end-diastolic volume (ml).

Nitroprusside was infused by a flow controlled pump, 20 minutes after the first left ventricular angiogram. The initial flow rate was 10 μg/min, and this was increased every 3 to 5 minutes to obtain a stable reduction of the mean aortic pressure. The reduction in the mean aortic pressure was less than 30 mmHg except in 2 patients in whom the initial mean aortic pressure was above 100 mmHg. The simultaneous decrease of the left ventricular end-diastolic pressure was less than 10 mmHg except in 4 patients in group 2 in whom the initial left ventricular end-diastolic pressure was above 20 mmHg.

Once the pressures had become stable the nitroprusside infusion rate was maintained at a constant rate; this rate differed greatly in each patient (Table).

Results

(1) A good correlation was observed between the angiographically derived stroke volume and that obtained from the dye dilution method. The regression equation was: dye method = 6·9 + 0·89 angio method ($n = 42$, $r = 0{\cdot}88$).

(2) Changes in heart rate, cardiac index, stroke volume, mean aortic pressure, total systemic vascular resistance, and ejection fraction. The heart rate did not change significantly in either group (Table). Significant increases in cardiac index and stroke volume were observed in group 2 only ($P < 0{\cdot}05$). Mean aortic pressure and total systemic vascular resistance decreased significantly in both the groups (MAP group 1 $P < 0{\cdot}01$, and group 2 $P < 0{\cdot}001$; total systemic vascular resistance $P < 0{\cdot}01$ for both). The ejection fraction did not alter in group 1, but it increased significantly in group 2 ($P < 0{\cdot}01$).

(3) Changes in left ventricular end-diastolic pressure and volume. The end-diastolic pressure

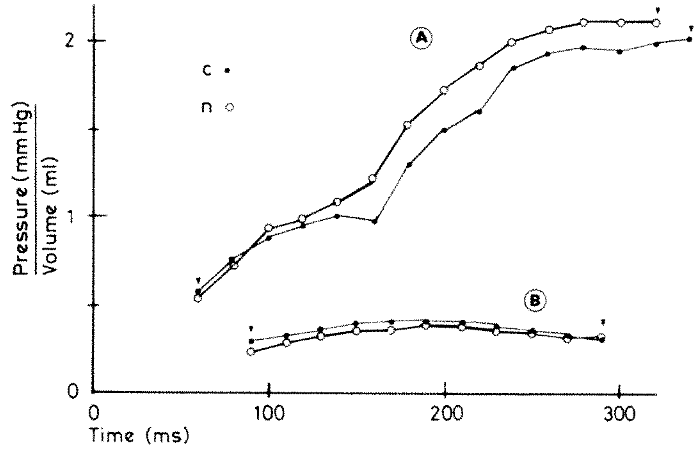

Fig. 1 *Example of the instantaneous pressure-volume ratio plotted against time during ejection before (c) and during (n) nitroprusside infusion in 2 patients. (A) Patient with a normal left ventricular performance. (B) Patient with a cardiomyopathy.* ▼, *onset and end of ejection.*

was lower in group 1 compared with group 2 ($P < 0{\cdot}01$). In both groups it decreased significantly ($P < 0{\cdot}001$), in group 1 by 3 mmHg and in group 2 by 9 mmHg. The absolute decrease in group 2 was higher, but the relative decrease (that is percentage change from control) was identical in both groups. Left ventricular end-diastolic volume decreased significantly in both the groups (group 1 $P < 0{\cdot}05$; group 2 $P < 0{\cdot}01$). In terms of absolute value the decrease was the same in both groups (27 and 26 ml, respectively). The relative decrease was lower in patients in group 2 ($P < 0{\cdot}05$) in whom the initial end-diastolic volume had been larger ($P < 0{\cdot}001$).

(4) Changes in left ventricular end-systolic pressure and volume. Left ventricular end-systolic pressure decreased significantly in both the groups (group 1 $P < 0{\cdot}001$; group 2 $P < 0{\cdot}01$); the relative decrease was identical. In terms of absolute values the decrease was greater in group 1 than in group 2 (33 and 20 mmHg, repectively, $P < 0{\cdot}01$). The basal end-systolic pressure was higher in group 1 compared with group 2 ($P < 0{\cdot}01$).

Left ventricular end-systolic volume decreased significantly in both the groups ($P < 0{\cdot}01$ for both), and the relative decrease was identical. In terms of absolute values the decrease was greater in group 2 compared with group 1 (39 and 12 ml, respectively, $P < 0{\cdot}05$); the initial left ventricular end-systolic volume was higher in group 2 ($P < 0{\cdot}001$).

Instantaneous systolic pressure-volume ratios during ventricular ejection were identical before and during nitroprusside infusion. Towards the end of systole, the pressure-volume ratio was practically constant (Fig. 1). Thus, even though ejection time

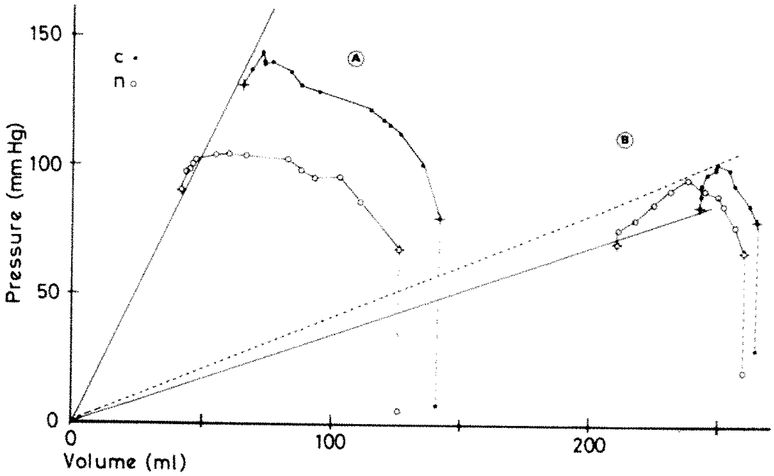

Fig. 2 *Example of the left ventricular pressure-volume diagrams before (c) and during (n) nitroprusside infusion in 2 patients (same patients as Fig. 1). (A) Patient with a normal left ventricular performance. (B) Patient with a cardiomyopathy.* +, *onset and end of ejection.*

decreased slightly, during nitroprusside, the $\frac{ESP}{ESV}$ ratio remained constant (3·6 and 3·5 in group 1; 0·5 and 0·5 in group 2) (Table). In patients in group 2 the $\frac{ESP}{ESV}$ ratio was significantly lower compared with group 1 patients ($P < 0·001$).

As the $\frac{ESP}{ESV}$ ratio was nearly the same before and during vasodilator infusion, a straight line was obtained which intersected near the origin and on which the pressure-volume diagrams ended (Fig. 2). For all the patients in group 1 and for 7 in group 2 the $\frac{ESP}{ESV}$ relations corresponded to the maximum value of instantaneous pressure-volume ratio. For 6 patients in group 2, the $\frac{ESP}{ESV}$ ratio was lower than the maximum systolic value.

Discussion

Nitroprusside has no direct positive inotropic effects on the myocardium (Chatterjee *et al.*, 1973). The effects of this agent in patients without coronary insufficiency are related to its peripheral effects on the arterial and venous systems and the resulting effects on the left ventricular loading conditions (Miller *et al.*, 1975; Rossen *et al.*, 1976).

The haemodynamic changes with nitroprusside in this study were similar to those reported previously. A drop in mean aortic pressure, left ventricular end-diastolic pressure, pulmonary wedge pressure, and systemic vascular resistance has been noted in normal subjects and in patients with arterial hypertension (Schlant *et al.*, 1962), acute myocardial infarction (Franciosa *et al.*, 1972; Chatterjee *et al.*, 1973), and chronic congestive heart failure (Miller *et al.*, 1975; Rossen *et al.*, 1976). A significant increase in cardiac output was found mainly in patients whose left ventricular filling pressures were high in the control state, remaining at the upper limit of normal during vasodilator therapy (Chatterjee *et al.*, 1973; Miller *et al.*, 1975; Rossen *et al.*, 1976). Conversely, if filling pressure decreased considerably a fall in cardiac output might result; this would be reversed by expansion of the circulating volume (Miller *et al.*, 1975).

As there were only minor changes in heart rate, changes in cardiac output were accompanied by changes in stroke volume. The changes in stroke volume after nitroprusside followed closely the respective variations in end-diastolic volume and end-systolic volume.

During nitroprusside infusion there was a consistent decrease in left ventricular end-diastolic pressure and volume. In group 2, there was a similar reduction in left ventricular end-diastolic volume to that in patients in group 1 resulting in a larger decrease in end-diastolic pressure; this probably indicated that the patients in group 2, whose left ventricular end-diastolic pressure was higher, were on a steeper portion of the passive left ventricular pressure volume relation. However, our study does not allow evaluations of changes in left ventricular distensibility during nitroprusside infusion.

During nitroprusside infusion there was a consistent decrease in left ventricular end-systolic volume and pressure. In the patients in group 2, the decrease in end-systolic pressure was lower and the decrease in end-systolic volume was greater than in patients in group 1. This is explained by the fact that $\frac{ESP}{ESV}$ ratio remained constant before and during nitroprusside infusion, and also by the lower value of this ratio observed in patients in the second group.

For a given contractile state peak isovolumic pressure is linearly related to volume over the physiological range of ventricular volumes in the isolated dog heart, and the slope of this peak pressure-volume line becomes steeper as contractile state is enhanced. For the same contractile state and for the same range of ventricular end-diastolic volumes, the isolated left ventricle of the dog contracting auxotonically (that is with no isovolumic period, volume decreasing throughout systole) reaches a maximum value of the pressure-volume ratio at end-systole that lies on the same straight line as obtained by isovolumic contraction (Suga and Sagawa, 1974).

In human subjects it is impossible to obtain isovolumic pressure-volume data. Nevertheless in a preliminary study in human subjects we have shown that the end-systolic pressure-volume ratio was independent of loading changes and related to the inotropic state of the left ventricle (Merillon *et al.*, 1977): the greater the end-systolic pressure volume ratio, the better the inotropic state.

Obviously stroke volume will increase only if end-systolic volume decreases more than end-diastolic volume. The decrease in left ventricular end-diastolic volume was similar in both groups. However as the slope of the end-systolic pressure-volume relation is lower in group 2, a slight decrease in left ventricular end-systolic pressure corresponds to a pronounced decrease in left ventricular end-systolic volume. Thus the stroke volume increased significantly only in patients from group 2.

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Blockade of cardiac and renal beta-receptors by low dose propranolol in normal subjects

Clues to its antihypertensive effect

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SUMMARY We studied the effects of oral propranolol administered in 2 low dose schedules (5 or 20 mg 8 hourly) and for a short term (30 to 36 hours) on heart rate, plasma renin activity, and arterial pressure, both at rest and after an isoprenaline challenge (8 mg i.v. over 2 min) in 6 normal subjects. Resting heart rate, plasma renin activity, and systolic pressure all fell significantly after the 5 mg dose and only small additional falls were observed when the dose was increased to 20 mg. The fall of diastolic pressure was not significant with 5 mg, but was significant with 20 mg. That beta-blockade occurred with these low doses was confirmed by diminished responses to isoprenaline. The isoprenaline-induced changes of heart rate, plasma renin activity, and diastolic pressure were reduced by 77, 80, and 65 per cent, respectively, by the 5 mg dose of propranolol, and by 89, 94, and 87 per cent by the 20 mg dose, suggesting that cardiac and renal receptors are equally sensitive to propranolol.

These data indicate a rapid blood pressure lowering action of low dose propranolol in normal subjects and suggest that this effect is in part at least a consequence of blockade of renal and/or cardiac beta-receptors. Our results also raise the possibility that much lower doses of propranolol than generally used may be clinically effective.

Despite the widespread use of beta-blockers in the treatment of hypertension, the exact mechanism by which they lower arterial pressure remains obscure. Some have argued that their action is attributable to the blockade of beta-receptors in the heart (Frohlich *et al.*, 1968; Pritchard, 1970) or in the kidneys (Bühler *et al.*, 1972; Casterfors *et al.*, 1973), while others have suggested that their action in hypertension results from effects not directly caused by beta-blockade, such as baroreceptor resetting (Pritchard and Gillam, 1969) or an action on the central nervous system (Offerhaus and Van Zweiten, 1974; Myers *et al.*, 1975). In support of the last two views are studies that indicate delay in the onset of the hypertensive relative to the beta-blocking effects (Pritchard, 1970) and studies suggesting that the hypotensive effect is only seen at doses considerably greater than those required to block peripheral beta-receptors (Zacharias, 1969; Michelakis and McAllister, 1972). There is very little information as to whether administration of propranolol can lower blood pressure in normotensive individuals, though recent reports have indicated that it may (Le Winter *et al.*, 1975; Miller *et al.*, 1975). In this present study we have administered propranolol in low doses and for a short term to normal subjects, to examine the effects of blockade of peripheral beta-receptors on arterial pressure, and have assessed the degree of beta-blockade by a standardised isoprenaline test (Davies *et al.*, 1977).

Subjects and methods

Six normal subjects who gave their informed consent participated. They were aged 26 to 35 years, were in good physical health, and on no medication. They were studied supine on 4 occasions at approximately the same time in the afternoon; the order in which the first 3 studies were conducted was randomised, while in each subject in a fourth study resting heart

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rate and arterial pressure only were determined. At least 7 days elapsed between studies. The basic procedure was similar for each study; the subjects lay supine in a quiet environment; a slow intravenous infusion of 0·9 per cent saline was established in a left arm vein to facilitate blood sampling and the infusion of isoprenaline. The subjects rested for 30 minutes with the infusion *in situ*; during the last 5 to 10 minutes heart rate and sphygmomanometrically measured arterial pressure were determined at 1 to 2 minute intervals until a steady baseline was established. Korotkof sounds I and IV were used to determine systolic and diastolic pressures, respectively, and the same mercury sphygmomanometer was used throughout. All measurements of heart rate and arterial pressure were made by the laboratory nurse who was unaware of the dosing sequence. A control sample for plasma renin activity was taken and then an infusion of 8 μg isoprenaline diluted in 10 ml saline was administered slowly by hand over 2 minutes. Heart rate and arterial pressure were determined at 1 minute intervals for 6 minutes and at 2 to 3 minute intervals for a further 15 minutes. Further samples for plasma renin activity were taken 5, 10, 15, and 20 minutes after the beginning of the isoprenaline infusion. In the studies with propranolol, either 5 or 20 mg was administered beginning at 7 to 8 a.m. of the day before study; medication was taken 8-hourly for a total of 5 doses, the last dose being taken some 90 minutes before study. A 24-hourly urine collection was made from noon of the day before study until noon of the study day.

Plasma renin activity was determined as previously described (Sealey and Laragh, 1975) and urinary sodium was determined by flame photometry.

DETERMINATION OF RESTING HEART RATE AND BLOOD PRESSURE

The means of at least 4 determinations of heart rate, systolic and diastolic pressure observed in the first control study were used to determine the resting values. The values so obtained were then compared with similar values obtained in the fourth study. If these mean values differed by more than 4 beats/min or by more than 4 mmHg, then the mean of the mean values so determined was used in subsequent calculations.

STATISTICS

Results are expressed as mean ± SEM and are analysed by Student's t test for paired data, each subject providing his own control basal and isoprenaline response data. The percentage reduction of the isoprenaline response is calculated by comparing the responses of heart rate and plasma renin activity on propranolol with that subject's control response.

Results

Neither propranolol nor isoprenaline resulted in any untoward effect in any subject. In the control study the subjects experienced mild palpitation and throbbing of the trunk, symptoms which were diminished considerably by both doses of propranolol.

EFFECT OF PROPRANOLOL ON BASAL VALUES (Fig.)

The mean control systolic pressure of 120 ± 6·5 mmHg was significantly ($t = 7{\cdot}01$, $P < 0{\cdot}001$) reduced to 114 ± 6 mmHg by the 5 mg dose, and to 109 ± 7 mmHg by the 20 mg dose ($t = 3{\cdot}42$, $P < 0{\cdot}01$). The decrease of diastolic pressure from 71·5 ± 2 mmHg to 67 ± 4 mmHg with the 5 mg dose was not significant, but the fall to 61·5 mmHg with the 20 mg dose ($t = 4{\cdot}24$, $P < 0{\cdot}01$) was significant. Heart rate fell from 72·0 ± 1·5 beats/min to 61 ± 1·5 beats/min with the 5 mg dose ($t = 9{\cdot}83$, $P < 0{\cdot}001$) and to 58 ± 3·5 with 20 mg ($t = 4{\cdot}17$, $P < 0{\cdot}01$). Plasma renin activity fell from 3·1 ± 0·7[1] μg/h per l to 1·8 ± 0·4 μg/h per l with the 5 mg dose ($t = 2{\cdot}17$, $P < 0{\cdot}05$) and to 1·6 ± 0·7 μg/h per l with the 20 mg dose ($t = 5{\cdot}42$, $P < 0{\cdot}001$). Urinary sodium excretion and serum potassium were unaffected by propranolol.

EFFECTS OF PROPRANOLOL ON RESPONSE TO ISOPRENALINE

In the control study, the mean increase in heart rate after isoprenaline was 43 ± 5 beats/min; after propranolol the mean increase was only 10 ± 2 beats/min for the 5 mg dose and 4·5 ± 1 beats/min for the 20 mg dose (5 mg and 20 mg vs control, $t = 6{\cdot}47$ and $6{\cdot}63$, respectively, $P < 0{\cdot}001$ for each, 5 mg vs. 20 mg, $t = 2{\cdot}69$, $P < 0{\cdot}025$). The mean increase in plasma renin activity in the control study was 3·6 ± 1 μg/h per l. This fell to 0·7 ± 0·1 μg/h per l after the 5 mg dose ($t = 3{\cdot}03$, $P < 0{\cdot}025$) and to 0·2 ± 0·01 μg/h per l after the 20 mg dose (control vs. 20 mg, $t = 3{\cdot}61$, $P < 0{\cdot}01$). The response after the 20 mg dose was significantly less than that after 5 mg ($t = 6{\cdot}5$, $P < 0{\cdot}001$). The mean isoprenaline-induced fall of diastolic pressure was 24 ± 4 mmHg in the control study; this was significantly attenuated to 8·5 ±2 mmHg ($t = 3{\cdot}1$, $P < 0{\cdot}025$) by the 5 mg dose of propranolol, and further to 3 ± 1 mmHg by the 20 mg dose. The

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[1] 1 μg/h per l ≈ 0·77 nmol/h per l.

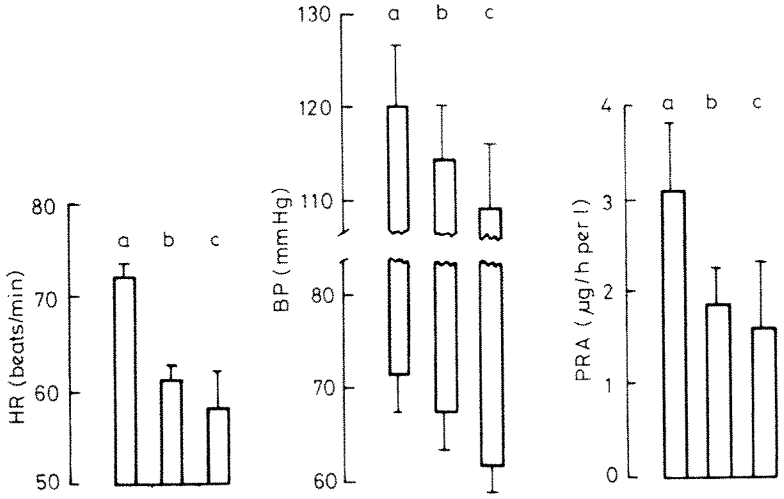

Fig. *Effect of propranolol on resting heart rate (HR), blood pressure (BP), and plasma renin activity (PRA) (a, control; b, propranolol 5 mg; c, propranolol 20 mg). Note that the major fall in heart rate and plasma renin activity occurred with the 5 mg dose.*

mean percentage reduction of the isoprenaline-induced changes of heart rate and plasma renin activity observed with the doses of propranolol employed amount to 77 ± 6 per cent and 89 ± 4 per cent, respectively, for heart rate (5 vs. 20, $t = 2{\cdot}19$, $P < 0{\cdot}5$) and to 80 ± 6 per cent and 94 ± 1 per cent, respectively for plasma renin activity (5 vs. 20, $t = 9$, $P < 0{\cdot}025$). The corresponding values for the blockade of diastolic pressure were 65 ± 11 per cent and 87 ± 4 per cent, respectively.

Discussion

This study describes some interesting, heretofore unrecognised, effects of low dose propranolol in normal subjects. Of particular interest is the effect of propranolol in a dose of only 5 mg 8-hourly (15 mg daily) in lowering both resting heart rate and plasma renin activity. Indeed, when the dose was increased fourfold to 20 mg 8-hourly (60 mg daily), only small additional falls in these variables were observed, suggesting that large, and possibly near maximal, blockade of resting heart rate and plasma renin activity can be obtained at very low doses of propranolol. This possibility is strengthened by the observation that 75 per cent or more of the isoprenaline-induced changes of heart rate and plasma renin activity are blocked by this dose. Consonant with this finding is the study of Leonetti *et al.* (1975) who treated patients with hypertension with propranolol in increasing doses from 40 to 160 mg daily. They found that near maximal falls of resting heart rate and of plasma renin activity were achieved at the 40 mg/day dose, which was the lowest dose they studied, there being relatively small additional falls when the dose of propranolol was increased stepwise to 160 mg daily. A further point of interest is the effect of propranolol on arterial pressure, a change that followed closely those of heart rate and plasma renin activity. Thus, systolic pressure fell by 6 mmHg on the lower dose and 11 mmHg on the higher, and similarly diastolic pressure fell on both doses. Our results, therefore, show that propranolol given in low doses can lower arterial pressure in normal subjects, and that this effect occurs within 36 hours.

A potential criticism of our study is that the small falls of arterial pressure that we have observed might be the result of a placebo effect or of observer bias. However, the order in which the studies were conducted was randomised to minimise these effects and the nurse-observer was unaware of the dosing sequence. Furthermore, the basal values of heart rate and arterial pressure were checked in the fourth study when no drugs were administered and no blood drawn. Indeed the extent of the falls of these variables with these doses was quite unexpected, and the effects on resting plasma renin activity and on the isoprenaline responses are unlikely to be susceptible to placebo effects or to observer bias. Furthermore, other workers have reported falls of arterial pressure in normal subjects. Thus, Le Winter *et al.* (1975) found a small but significant fall in arterial pressure after the administration of propranolol (160 mg daily for 2 weeks) to normal young subjects, and Miller *et al.* (1975) found that blood pressure fell significantly in normotensive patients who were receiving propranolol for angina pectoris. In the context of these earlier studies, our results extend this observation to a lower dose level.

To what extent does this study clarify our understanding of the mechanisms by which propranolol lowers arterial pressure? By using very small doses of propranolol administered short term, it can be assumed that the site of action is limited to peripheral beta-receptors, since it is generally agreed that such blood pressure lowering effect as propranolol may have, due to a central action, is seen with relatively large doses (Hollifield *et al.*, 1975). In common with Leonetti *et al.* (1975) we have observed striking reductions of heart rate and plasma renin activity after doses of propranolol far below those required to exert an effect on the central nervous system (Offerhaus and Van Zweiten, 1974; Hollifield *et al.*, 1975). Moreover, in the present study these effects were accompanied by a small but significant fall of arterial pressure, and it seems probable that this is also a consequence of peripheral beta-blockade. Two possible mechanisms have been proposed to explain this blood pressure lowering effect: first, by blockade of cardiac receptors, reducing heart rate and cardiac output, and secondly, by blockade of renal receptors reducing plasma renin activity. The blood pressure lowering effect of propranolol has been attributed to a reduction of cardiac output by a number of groups (Ulrych *et al.*, 1968; Johnsson *et al.*, 1969; Pritchard *et al.*, 1970; Sannerstedt *et al.*, 1970), though more recently the Cleveland group, who were the main proponents of this view, have found that the antihypertensive response was predictable neither by control measurements of cardiac function nor by changes in cardiac function induced by propranolol therapy (Tarazi and Dustan, 1972). The alternative view, that propranolol's antihypertensive effect is mediated by its renin-lowering action, was first suggested by Bühler *et al.* (1972). While this view has been supported by several studies (Casterfors *et al.*, 1973; Hansson and Zweifler, 1974), it has been contested by others (Birkenhäger *et al.*, 1971; Stokes *et al.*, 1974; Bravo *et al.*, 1975). An argument that has figured prominently in opposing the view that propranolol can lower blood pressure by its renin-lowering action is the apparent temporal dissociation between the fall of plasma renin activity, which occurs early, and the fall of arterial pressure, which some workers have suggested is delayed (Frohlich *et al.*, 1968; Pritchard, 1970). Manifestly this is not necessarily the case, as has been shown in this and other studies (Ulrych *et al.*, 1972; Leonetti *et al.*, 1975; Fitzgerald, 1976; Stumpe *et al.*, 1976; Taylor *et al.*, 1976). Similarly, the view held by some workers (Pritchard and Gillam, 1969; Zacharias, 1969; Michelakis and McAllister, 1972) that a higher dose of propranolol is required for the antihypertensive effect compared with the renin-lowering effect, which has also been used as evidence against these effects being related, is not supported by our study or by that of Leonetti *et al.* (1975). While this present study in no way excludes a second influence at high doses, it does define a close association between the blood pressure lowering effect of propranolol and peripheral beta-blockade. The relative contributions of the effects on cardiac and renal receptors require further dissection.

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Uptake of catecholamines by human cardiac muscle in vitro[1]

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SUMMARY Noradrenaline uptake was studied using heart muscle from 102 patients undergoing cardiac surgery. Slices of right atrium were incubated in Krebs-Henseleit solution containing $1{\cdot}3 \times 10^{-7}$ M ^{3}H-noradrenaline. Uptake was lower in failing heart muscle and was inhibited not only by increasing the noradrenaline concentration in the incubating medium but also by adding the drugs desmethylimipramine, amitryptyline, and ouabain.

The adrenergic neurone possesses an efficient uptake mechanism whose properties are well known. Noradrenaline is the preferred substrate but the process exhibits stereochemical and structural specificity so that adrenaline and dopamine are also substrates whereas isoprenaline is not. Uptake is energy and temperature dependent; it obeys enzyme kinetics and is inhibited by a range of drugs including cocaine, the tricyclic antidepressants, and the cardiac glycosides (Iversen, 1967, 1973; von Euler, 1972). Neuronal uptake of adrenaline and noradrenaline removes these catecholamines from the extracellular space and thus terminates their effects.

This paper describes, for the first time, the neuronal uptake of catecholamines by human cardiac muscle. The experiments were performed in vitro.

Patients and methods

(1) PATIENTS

Samples of cardiac muscle were obtained from 102 patients (64 male and 38 female) undergoing open heart surgery at the National Heart Hospital or Harley Street Clinic. Their ages ranged from 7 to 70 years (mean 48·4). Only patients undergoing aortic or mitral valve surgery or coronary artery bypass operations were studied and they were divided into those with and those without cardiac failure as diagnosed by the referring physician; the former had all been treated with digoxin and diuretics. Right atrial muscle was taken from the atrial appendage, and left ventricular muscle from the papillary muscle of patients undergoing mitral valve replacement.

(2) CATECHOLAMINE UPTAKE EXPERIMENTS

The samples were collected in ice-cold Krebs-Henseleit solution containing 2 g glucose, 20 mg ascorbic acid, and 10 mg ethylenediaminotetraacetic acid per litre; the calcium concentration was 1·275 M (Iversen, 1963). The samples were cut into 0·5 mm slices using a tissue slicer and preincubated in the solution at 37° C for 15 min. Both before collection and throughout the experiments the Krebs-Henseleit solution was gassed with 5 per cent carbon dioxide and 95 per cent oxygen. Blanks were prepared by incubating the tissue at 0° C. Estimations were made in triplicate. ^{3}H-noradrenaline was added to give the desired final concentration in 5 ml of solution; any drugs were added at the beginning of the preincubation time.

After incubation the slices were harvested by filtration, washed with a further 15 ml of Krebs-Henseleit solution, and weighed. The slices were dissolved in 1 ml Soluene 350 (Packard Inst. Co.) at 50° C and their radioactivity counted in a Packard TRICARB liquid scintillation spectrometer using 10 ml Dimilume (Packard Inst. Co.) as the scintillant.

The results were corrected for quenching using the automatic external standard and expressed as a concentration ratio by comparison of disintegrations per minute (d.p.m.) per mg tissue and d.p.m. per μl medium.

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(3) DRUGS AND REAGENTS

DL-(7-3H) noradrenaline hydrochloride (specific activity 15 Ci/mmol, DL-(7-3H)), isoprenaline (specific activity 10 Ci/mmol and DL-(7-3H)), adrenaline (specific activity 14·3 Ci/mmol) were supplied by the Radiochemical Centre, Amersham, U.K. The following drugs were kindly donated by the pharmaceutical industry—desipramine HCl (Geigy), lignocaine HCl (Astra), amitriptyline HCl (Merck, Sharp and Dohme), dl propranolol HCl (Imperial Chemical Industries Ltd.); ouabain was supplied by British Drug Houses.

(4) STATISTICS

Results in the text are expressed as the mean ± standard deviation. Their significance was determined using Student's t test.

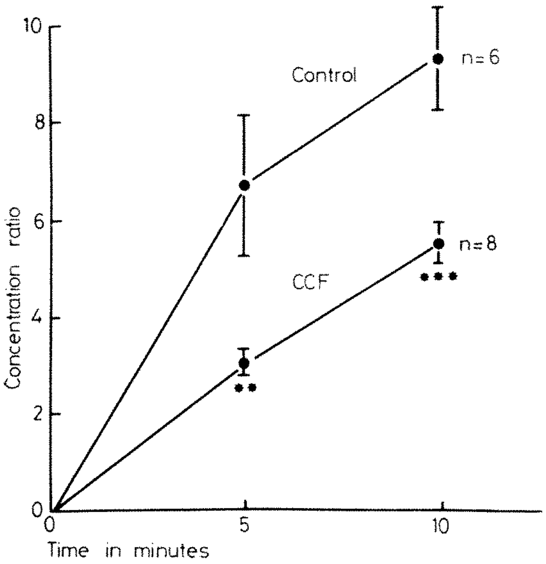

Fig. 1 *Uptake of ^{3}H-noradrenaline by human right atrial muscle from patients with and without congestive cardiac failure (CCF). The results are expressed as the mean ± SEM of n experiments. *$P < 0{\cdot}05$, **$P < 0{\cdot}01$, ***$P < 0{\cdot}001$ in this and subsequent figures.*

Table 1 *^{3}H-noradrenaline uptake by human right atrium in vitro*

Time (min)	*Concentration ratio mean ± SD*	
	Aortic valve replacement	*Mitral valve replacement*
5	2·72 ± 0·98	3·07 ± 1·24
10	4·75 ± 1·52	5·56 ± 1·87
20	9·22 ± 3·89	9·07 ± 3·66
40	14·60 ± 3·20	14·06 ± 3·64
60	20·94 ± 6·14	20·42 ± 6·15
	n = 7	n = 9

Results

After 10 minutes incubation in Krebs-Henseleit solution containing $1{\cdot}3 \times 10^{-7}$ M ^{3}H-noradrenaline the concentration ratio for a 'control' group of 6 patients was 9·28 ± 2·84. These patients were undergoing coronary artery bypass operations, and had normal cardiac function at rest; none had ever received treatment with digoxin or diuretics. In 8 patients with cardiac failure undergoing aortic or mitral valve replacement the corresponding concentration ratio was 5·46 ± 1·53 (Fig. 1). When the experiments were repeated using ^{3}H-sorbitol, no significant difference between the two groups was detected; the mean concentration ratio for the two groups combined was 0·36 ± 0·01 (n = 9). There was no difference between the samples from patients undergoing aortic, as compared with mitral valve replacement though the incubation time was extended to one hour (Table 1).

Slices of left ventricular muscle accumulated $1{\cdot}3 \times 10^{-7}$ M ^{3}H-noradrenaline more slowly than right atrial muscle so that after one hour of incubation the concentration ratio was 8·86 ± 3·12. This was significantly lower than the concentration ratio obtained for right atrial samples taken from patients with cardiac failure, which was 20·65 ± 6·15 (Fig. 2).

The effect of noradrenaline concentration on the initial uptake velocity was examined using right atrial samples from patients with cardiac failure and a 5-minute incubation time; the concentration ratio fell as the noradrenaline concentration in the incubating medium increased (Table 2). While it

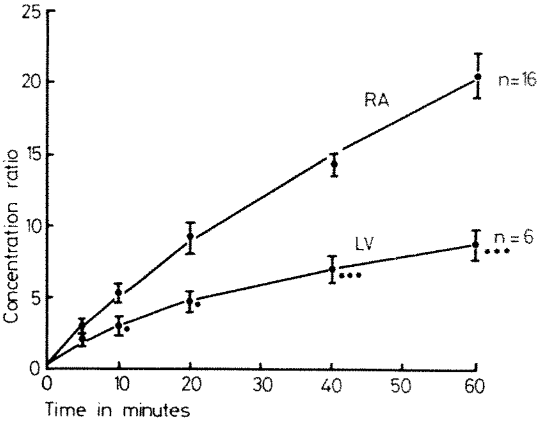

Fig. 2 *^{3}H-noradrenaline uptake by human right atrial (RA) and left ventricular (LV) muscle taken from patients with congestive cardiac failure.*

Table 2 *Effect of increasing noradrenaline concentration on uptake*

Noradrenaline concentration (μM)	*Concentration ratio*	*Uptake velocity nm/min per g*
0·13	4·12 ± 0·56	0·08
0·30	3·14 ± 0·63	0·12
0·90	2·53 ± 0·59	0·26
3·00	1·95 ± 0·34	0·51
9·00	1·63 ± 0·34	0·96
15·00	1·58 ± 0·40	1·45
	n = 8	

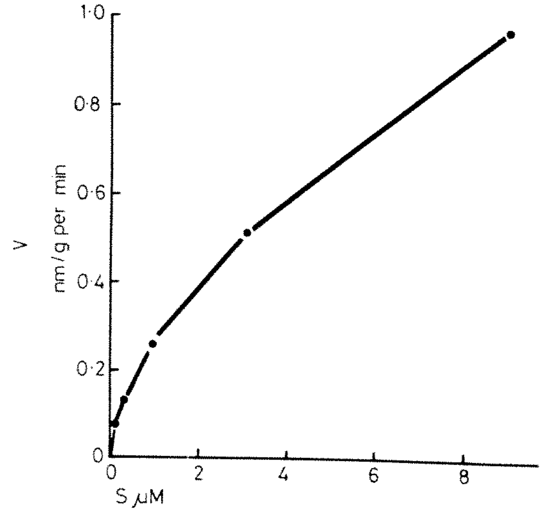

Fig. 3 *Initial velocity of noradrenaline uptake (V) plotted against substrate concentration (S) for right atrial muscle slices taken from patients with congestive cardiac failure.*

was possible to calculate the initial uptake velocity, the results obtained using ^{3}H-noradrenaline concentrations over 3 μM were less accurate as the concentration ratios approached the blank value (Fig. 3). Nevertheless, the uptake velocity did not increase linearly as the noradrenaline concentration was increased and a reciprocal plot of the 0·3, 0·9, and 3·0 μM values approximates to a straight line; the Michaelis constant and maximum uptake velocity were 1·5 μM and 0·7 nmol/min per g, respectively (Fig. 4).

The uptake of 1·3 × 10^{-7} ^{3}H-noradrenaline by slices of right atrial muscle was inhibited by the tricyclic antidepressants desipramine and amitriptyline (Table 3); lignocaine and propranolol were without effect. Ouabain inhibited noradrenaline uptake in a group of 4 patients undergoing coronary artery bypass surgery, none of whom had ever received treatment with digitalis glycosides (Table 4). The same effect could be detected in patients with cardiac failure but the inhibition was less pronounced.

Adrenaline was taken up by slices of right atrial muscle from patients with cardiac failure though the concentration ratios were lower than those for noradrenaline. After 10 minutes of incubation with 1·3 × 10^{-7} M adrenaline the ratio was 3·30 ± 0·56 (n = 7); after 10 minutes of incubation in the presence of 10^{-6} M desipramine the concentration ratio was 1·58 ± 0·24. 10^{-5} M isoprenaline was not

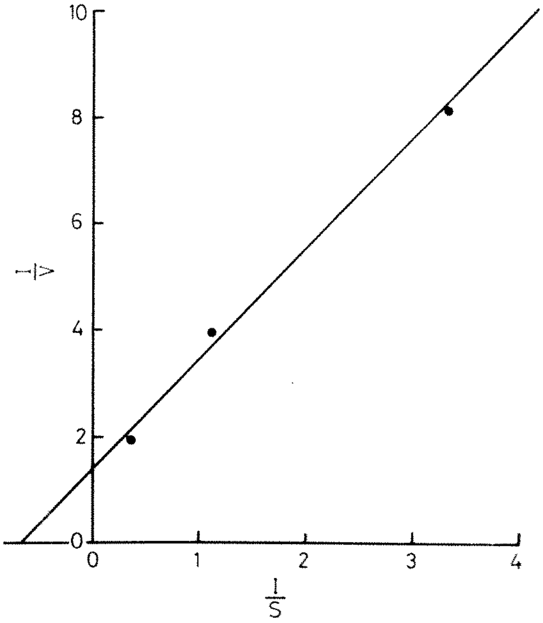

Fig. 4 *Lineweaver Burke plot of Fig. 3.*

Table 3 *Effect of drugs on noradrenaline uptake*

	Concentration ratio	*P*
Control	6·72 ± 1·84	
Desmethylimipramine	2·18 ± 0·46	< 0·001
Amitriptyline	2·99 ± 0·47	< 0·001
Lignocaine	6·44 ± 2·19	NS
Propranolol	6·14 ± 1·95	NS
	n = 8	

All drug concentrations = 10^{-6} M

Table 4 *Effect of ouabain on noradrenaline uptake*

	Concentration ratio
Control	8·43 ± 0·36
Ouabain 10^{-8} M	6·28 ± 0·60
Ouabain 10^{-6} M	5·51 ± 0·09
Ouabain 10^{-4} M	4·93 ± 0·43
	n = 4

taken up and the concentration ratios did not differ significantly from the blanks.

Discussion

Noradrenaline uptake was demonstrable at low external amine concentrations, was temperature sensitive, and was inhibited by increasing the external amine concentration and by desipramine, amitriptyline, and ouabain; adrenaline was taken up whereas isoprenaline was not. These are the features of the neuronal uptake process and it, therefore, appears that noradrenaline was being taken up by the sympathetic neurones of the right atrial samples. This study is the first demonstration of the neuronal uptake process in human cardiac muscle. It is likely that the techniques we have used would underestimate the velocity of the uptake process which may be more rapid in vivo (Petch, 1977).

The depressant effect of cardiac failure on the neuronal uptake process has been shown in the heart muscle of experimental animals (Fischer *et al.*, 1965; Spann *et al.*, 1965; Sassa, 1971); it is also suggested by the results obtained in the present study. However, all patients with cardiac failure had received treatment with digitalis glycosides whose inhibitory effect on ^{3}H-noradrenaline uptake was confirmed in a separate experiment. Thus, it is possible that both the presence of cardiac failure and treatment with cardiac glycosides contributed to the depression of noradrenaline uptake observed in the samples of right atrial muscle taken from patients undergoing valve replacement and the relative importance of the two factors cannot be determined.

Regional differences in the activity of the neuronal uptake process, like the differences in catecholamine concentration, reflect the density of sympathetic innervation (Iversen, 1967). The greater uptake of ^{3}H-noradrenaline by human right atrial muscle slices compared with left ventricular muscle was thus in keeping with our earlier observation of a higher noradrenaline concentration in the former (Petch and Nayler, 1979).

The clinical importance of the neuronal uptake process is that it determines the concentration of catecholamines at the cardiac adrenoceptor. Thus those factors that impair neuronal uptake such as an autonomic neuropathy, cardiac failure, and ischaemia, and the presence of digitalis glycosides or tricyclic antidepressants, will potentiate the cardiac effects of adrenaline and noradrenaline.

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Concentration of catecholamines in human cardiac muscle[1]

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SUMMARY A trihydroxyindole fluorescent technique was used to measure the concentration of catecholamines in heart muscle taken from 42 patients undergoing open heart surgery. Noradrenaline was the dominant catecholamine and its depletion in the failing heart was confirmed. The distribution of catecholamines within the heart was such that the highest value, 2·64 ± 0·68 μg/g, was found in the non-failing right atrium and the lowest, 0·53 ± 0·40 μg/g, in the failing left ventricle.

The effects of sympathetic stimulation on the heart are mediated by the neurotransmitter, noradrenaline. This catecholamine is present in relatively large quantities in heart muscle but its concentration is reduced in patients with heart failure (Chidsey *et al.*, 1963; Gertler *et al.*, 1970; DeQuattro *et al.*, 1973). Little is known about the concentration and distribution of catecholamines in normal heart muscle. The data presented in this paper suggest that the myocardial catecholamine concentration may be higher than had been supposed in the past and that the distribution is similar to that found in the hearts of experimental animals.

Patients and methods

Samples of heart muscle (atrial appendage or ventricular papillary muscle unless stated) were obtained from 42 patients undergoing open heart surgery at the National Heart Hospital. There were 25 men and 17 women; their ages ranged from 3 to 66 years (mean 43·5).

The patients were grouped either according to their surgical diagnosis or into those with, and those without, cardiac failure. The diagnosis of failure was established by the referring physician and all patients with this diagnosis had received treatment with digoxin and diuretics; patients with coronary artery disease had all received treatment with beta-adrenergic antagonists, usually propranolol. Other drugs which were given routinely included the premedicating agents papaveretum and scopolamine, the anaesthetics methohexitone and nitrous oxide, and the antibiotics gentamycin and flucloxacillin.

Catecholamines were assayed by a trihydroxyindole fluorescent technique similar to that described by Anton and Sayre (1962). The only important difference was that sodium carbonate was used to adjust the *p*H when the catecholamines were being adsorbed onto the alumina. The differential assay for adrenaline and noradrenaline was performed by developing the fluorescence at *p*H 6·5 and 3·5. No attempt was made to differentiate dopamine from noradrenaline. Some drugs cause fluorescence *in vitro* and thus interfere with this technique. Carruthers *et al.* (1970) showed that this did not apply to such drugs as propranolol, digoxin, and papaveretum, but this point was examined using a variety of blank preparations and the absence of extraneous fluorescence was confirmed (Petch, 1977).

The assays were performed in duplicate using healthy fat-free myocardium; the absence of fat and fibrous tissue was confirmed by histological examination in a random sample of specimens. The results are expressed as the mean ± standard deviation per gram myocardium (wet weight). Student's t test was used to determine the significance of the results except in Table 3 where the difference between the groups was examined using a one-way analysis of variance.

Results

In all samples the dominant catecholamine was noradrenaline; only small amounts of adrenaline were found usually amounting to about 10 per cent of the total. The depletion of total catecholamines

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Table 1 *Concentration of catecholamines in human right atrium μg/g (mean ± SD)*

	Number	*Total*	*Noradrenaline*	*Adrenaline*
No cardiac failure	11	2·38 ± 0·65	2·16 ± 0·63	0·22 ± 0·12 (n = 11)
Cardiac failure	19	1·17 ± 0·45	1·06 ± 0·51	0·11 ± 0·08 (n = 19)
Probability		< 0·001	< 0·001	NS

Table 2 *Right atrial catecholamine concentration—effect of atrial fibrillation μg/g (mean ± SD)*

	Number	*Total*	*Noradrenaline*	*Adrenaline*
Sinus rhythm	7	1·39 ± 0·34	1·34 ± 0·53	0·19 ± 0·09
Atrial fibrillation	12	1·08 ± 0·44	0·90 ± 0·42	0·14 ± 0·09
Probability		< 0·01	< 0·01	NS

Table 3 *Right atrial catecholamine concentration μg/g (mean ± SD)*

Diagnosis	*Number*	*Total*	*Noradrenaline*	*Adrenaline*
Coronary artery disease	7	2·64 ± 0·68	2·38 ± 0·67	0·25 ± 0·12
Open mitral valvotomy	2	2·06	1·81	0·25
Aortic valve replacement	7	1·85 ± 0·70	1·64 ± 0·52	0·21 ± 0·09
Mitral valve replacement	5	1·11 ± 0·49	1·01 ± 0·49	0·09 ± 0·04
Multiple valve surgery	5	1·04 ± 0·28	0·83 ± 0·37	0·21 ± 0·10
Atrial septal defect	3	0·97 ± 0·29	0·88 ± 0·27	0·09 ± 0·01
Probability		< 0·001	< 0·005	< 0·05

Table 4 *Right atrial catecholamine concentration—effect of surgery μg/g (mean ± SD)*

	Number	*Total*	*Noradrenaline*	*Adrenaline*
Before	4	2·29 ± 1·06	2·01 ± 0·99	0·27 ± 0·09
After	4	2·25 ± 0·81	1·92 ± 0·82	0·33 ± 0·09
Probability		NS	NS	NS

Mean bypass time = 63 minutes.

Table 5 *Left ventricular catecholamine concentration μg/g (mean ± SD)*

Diagnosis	*Number*	*Total*	*Noradrenaline*	*Adrenaline*
Mitral valve replacement	11	0·53 ± 0·40	0·46 ± 0·37	0·07 ± 0·04
Aortic valve replacement	1	1·89	1·57	0·32
Coronary artery disease	1	1·11	1·07	0·04
Hypertrophic cardiomyopathy	1	1·06	0·98	0·08
Hypertrophic cardiomyopathy + failure	1	0·27	0·24	0·03

Table 6 *Right ventricular catecholamine concentration μg/g*

Diagnosis	*Number*	*Total*	*Noradrenaline*	*Adrenaline*
Fallot's tetralogy	1	1·06	0·91	0·15
Ventricular septal defect	1	2·19	2·06	0·13
Pulmonary valve replacement	1	1·61	1·57	0·04
Hypertrophic cardiomyopathy	1	0·81	0·71	0·10
Trucuspid valve replacement + mitral valvotomy (+ failure)	1	0·65	0·62	0·03

and of noradrenaline in the right atrial samples taken from patients with cardiac failure was confirmed (Table 1). In the cardiac failure group the presence of atrial fibrillation was associated with a lower catecholamine concentration (Table 2). If the patients are grouped according to their surgical diagnosis (Table 3) then it can be seen that those patients with coronary artery disease, who were deliberately selected because they had normal cardiac function, had the highest values, whereas those undergoing surgery for haemodynamic reasons had lower values. In addition to those results given in Table 3, the right atrial catecholamine concentration was examined in patients with two other conditions. A patient with hypertrophic cardiomyopathy who did not have cardiac failure had values for the total noradrenaline and adrenaline concentrations of 2·29, 2·20, and 0·09 μg/g, respectively. In 2 patients with an atrial myxoma and cardiac failure, the corresponding values were 0·87, 0·75, and 0·12 μg/g, respectively.

The absence of any significant change in the right atrial catecholamine concentration during cardiopulmonary bypass (Table 4) allowed a direct comparison of the right atrial and left ventricular catecholamine concentration to be made in 9 patients undergoing mitral valve replacement. In these 9 patients the total right atrial and left ventricular catecholamine concentrations were 1·22 ± 0·59 and 0·66 ± 0·50 μg/g, respectively ($P < 0{\cdot}01$); the corresponding figures for the noradrenaline concentrations were 1·11 ± 0·59 and 0·55 ± 0·43 μg/g, respectively ($P < 0{\cdot}01$). A comparison of right and left atria in 3 patients showed the mean total catecholamine concentration in both chambers to be similar at 1·03 and 1·40 μg/g, respectively. In 2 patients samples were obtained from the right atrium and right ventricle and in both the catecholamine concentration was higher in the right atrium.

In the left ventricle the lowest catecholamine concentrations were found in those patients undergoing mitral valve replacement (Table 5). A higher value was found in one patient with coronary artery disease. Here the sample was taken from a rim of healthy myocardium surrounding an area of fibrous tissue that was being resected during a coronary bypass operation. Higher values were also found in 3 other patients whose samples were taken from the hypertrophied outflow tract of the left ventricle though in these 3 patients the lowest value was again found in the patient with cardiac failure. The same pattern was observed in the right ventricle (Table 6). The highest value was found in a child undergoing an elective closure of a ventricular septal defect in whom an anomalous parietal muscle band was removed; the lowest value was found in a patient with chronic rheumatic heart disease undergoing mitral and tricuspid valve surgery.

Discussion

The sympathetic neurotransmitter, noradrenaline, is the dominant catecholamine in all peripheral mammalian tissues (Holzbauer and Sharman, 1972). Though there are important species differences the catecholamine concentration in experimental animals is higher in the right heart as compared with the left, and higher in the atria relative to the ventricles (Shore *et al.*, 1958; Muscholl, 1959; Angelakos *et al.*, 1963). The distribution of catecholamines within the walls of the cardiac chambers is uniform, and there is good evidence to show that the noradrenaline is stored in the adrenergic neurones so that the noradrenaline concentration reflects the density of sympathetic innervation (Angelakos, 1965; Iversen, 1967).

Any sustained increase in cardiac work leading to hypertrophy or failure is associated with a depletion of the myocardial catecholamine stores. This was first recognised by Meerson in rabbits subjected to aortic constriction and has been amply confirmed for a variety of experimental animal models (Meerson *et al.*, 1963; Fischer *et al.*, 1965; Spann *et al.*, 1965; Vogel *et al.*, 1969). The catecholamine depletion affects all cardiac chambers and is related to the severity and duration of the haemodynamic load; it appears to be peculiar to the adrenergic neurones of the myocardium since other tissues are not affected. In the experiments of Vogel *et al.* (1969) the noradrenaline depletion was shown to be reversible.

In patients with cardiac failure the myocardial catecholamine concentration is reduced. Chidsey *et al.* (1963) found a mean value of 0·53 μg/g in right atrial specimens taken from patients with chronic congestive failure, compared with a mean value of 1·82 μg/g in a 'control' group of patients undergoing surgery for such lesions as atrial and ventricular septal defects. Gertler *et al.* (1970) and DeQuattro *et al.* (1973) reported that the noradrenaline depletion was more pronounced in those patients with more severe symptoms. However, all these patients from previous studies had some haemodynamic lesion and only those patients with coronary artery disease in the present study had normal cardiac function. If their right atrial catecholamine concentration of 2·64 μg/g approaches the normal value for human right atrium, it implies a rich sympathetic innervation. The administration of beta-adrenergic antagonists is unlikely to have affected this value as the evidence from experimental animals suggests that propranolol has little effect on the myocardial noradrenaline concentration (Westfall, 1967; Lemner and Saller, 1974).

The variation in the right atrial catecholamine concentration found in the present study is best explained by postulating that in man, as in experimental animals, a sustained increase in cardiac work is associated with progressive noradrenaline depletion. Thus, those patients undergoing aortic valve replacement had higher values than those undergoing mitral valve replacement because they were operated upon earlier in the natural history of their disease. Similarly patients with an atrial septal defect, though not in 'cardiac failure', had had at least a twofold increase in blood flow through the right heart from birth and consequently low right atrial catecholamine concentrations. This hypothesis may also explain the variation in catecholamine concentration found in ventricular muscle. Nevertheless, the left ventricular levels were much lower than the right atrial. Since this distribution is similar to that found in experimental animals, it seems likely that the right atrium is more richly supplied with adrenergic neurones than the left ventricle.

The cause of the noradrenaline depletion in the failing heart is not clear but a number of factors may be involved including depressed synthesis, as shown by reduced tyrosine hydroxylase activity (Pool *et al.*, 1967; DeQuattro *et al.*, 1973), impaired neuronal uptake of noradrenaline (Spann *et al.*, 1965; Petch and Nayler, 1979), and excessive noradrenaline release after intense sympathetic stimulation. Furthermore, the administration of digoxin may exacerbate the noradrenaline loss since it is a known inhibitor of the neuronal uptake process (Iversen, 1973) though its effect on the myocardial catecholamine concentration in experimental animals with normal hearts is slight (Forster and Rosler, 1967; Harvey, 1975). These abnormalities may be regarded as part of a general depression of sympathetic nerve function which occurs in the failing heart. This depression is also reflected in the physiological behaviour of the sympathetic neurone since the failing heart is unable to respond normally to sympathetic stimulation despite its ability to respond to exogenous catecholamines (Covell *et al.*, 1966; Goldstein *et al.*, 1975).

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Nongenetically transmitted disproportionate ventricular septal thickening associated with left ventricular outflow obstruction

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SUMMARY Clinical, haemodynamic, and morphological features are described in 2 patients with disproportionate ventricular septal thickening, left ventricular outflow obstruction with systolic anterior motion of the anterior mitral leaflet, and either acquired or congenital heart disease. The disproportionate septal thickening in these patients appeared to be secondary to their underlying cardiac disease rather than a manifestation of genetically transmitted hypertrophic cardiomyopathy. One patient with combined aortic and mitral stenosis had severe systolic anterior motion of the anterior mitral leaflet and a residual large systolic pressure gradient between left ventricle and systemic artery after aortic valve replacement. In this patient the systolic anterior motion was evident in the presence of mitral valve stenosis. The other patient with mild aortic stenosis and a previously repaired coarctation of the aorta also had mild systolic anterior motion and a small subaortic systolic pressure gradient. Hence, these 2 patients demonstrate that disproportionate septal thickening secondary to acquired or congenital heart disease may be associated with left ventricular outflow obstruction and systolic anterior motion of the anterior mitral leaflet.

Hypertrophic cardiomyopathy is a disease of cardiac muscle that is characterised by a disproportionately thickened ventricular septum containing numerous disorganised cardiac muscle cells (Teare, 1958; Menges *et al.*, 1961; Abbasi *et al.*, 1972; Ferrans *et al.*, 1972; Abbasi *et al.*, 1973; Clark *et al.*, 1973; Henry *et al.*, 1973; Roberts, 1973; Maron *et al.*, 1974) and is usually transmitted as an autosomal dominant trait (Clark *et al.*, 1973). While the majority of patients with hypertrophic cardiomyopathy have no obstruction to left ventricular outflow (Epstein *et al.*, 1974), others may show dynamic outflow obstruction associated with systolic anterior motion of the anterior mitral leaflet (Shah *et al.*, 1969; Epstein *et al.*, 1974).

Disproportionate septal thickening (Maron *et al.*, 1977a) or clinically evident hypertrophic cardiomyopathy (Parker *et al.*, 1969; Block *et al.*, 1973; Nanda *et al.*, 1974; Bloom *et al.*, 1975; Johnson *et al.*, 1975) may also occur occasionally in patients with acquired or congenital heart diseases. In such patients the septal thickening, rather than a manifestation of genetically transmitted hypertrophic cardiomyopathy, is probably secondary to the underlying haemodynamic state; obstruction to left ventricular outflow or systolic anterior motion of the anterior mitral leaflet is absent (Maron *et al.*, 1977a).

This report describes the unusual clinical and morphological features in 2 patients with disproportionate septal thickening. In each of these patients left ventricular outflow obstruction and systolic anterior motion of the anterior mitral leaflet was present, but the disproportionate thickening of ventricular septum appeared to be secondary to underlying congenital heart disease in one patient and acquired heart disease in the other patient.

Case 1

A 67-year-old woman was first seen at the National Heart, Lung, and Blood Institute (NHLBI) because of valvular heart disease. She had a 'strep throat' at age 26; a heart murmur was heard shortly thereafter. The patient led an active, normal life until age 60 when she began to experience angina pectoris and lightheadedness. The patient remained stable until

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age 66 when she experienced dyspnoea and fatigue on exertion and orthopnoea. At admission to the NHLBI 7 months later, she was judged to be in functional class III.

On examination, a harsh, grade 4/6 systolic ejection murmer was heard loudest in the second right intercostal space and radiated to the carotids. A high-pitched, grade 3/6 decrescendo diastolic murmer was present along the left sternal border. A grade 2/6 mid-late diastolic rumble was also present at the apex. S_2 was single. An opening snap was not present. Chest radiograph showed enlargement of the left ventricle and left atrium and normal pulmonary vascular markings. Electrocardiogram showed left ventricular hypertrophy with 'strain' pattern and left atrial enlargement. On echocardiogram, ventricular septal thickness was 22 mm and posterobasal left ventricular wall thickness was 16 mm. The septal-free wall ratio was 1·4, which met our criteria for disproportionate septal thickening (that is, septal free-wall ratio $\geq 1{\cdot}3$) (Henry *et al.*, 1973; Maron *et al.*, 1977a). Left ventricular transverse dimension in diastole was normal (38 mm), left atrial transverse dimension was increased (46 mm), and aortic root diameter was normal (28 mm). The mitral valve was positioned anteriorly in the left ventricular cavity, as evidenced by an abnormal mitral valve position index of 1·7 (normal, $< 0{\cdot}3$) (Henry *et al.*, 1975). The mitral valve leaflets were not imaged adequately to judge the presence or absence of systolic anterior motion of the anterior mitral leaflet.

Haemodynamic data from the patient's two cardiac catheterisations are summarised in the Table. At the initial catheterisation (age 66; 8 October 1974) the patient showed a pronounced peak systolic pressure gradient of 80 mmHg across the aortic valve and a critically reduced aortic valve index (0·2 cm^2/m^2). A small 5 mmHg mean diastolic gradient was present across the mitral valve and the mitral valve index was 1·8 cm^2/m^2. Left ventriculography showed normal ventricular wall motion and no mitral regurgitation; ejection fraction was 0·80. Because of the patient's clinical and haemodynamic findings, aortic valve replacement was performed one week later. At operation, the aortic valve was tricuspid, severely stenotic, and calcified. A no. 19 Björk-Shiley prosthesis was inserted. The mitral leaflets, examined via the left atrium, were thickened, mobile, and free of calcium. The orifice had a diameter of about 4 cm.

Over the next 7 months the patient continued to experience exertional dyspnoea and fatigue. A second cardiac catheterisation (aged 67; 12 May 1975) was performed and showed a persistent 80 mmHg gradient between the left ventricle and femoral artery. In addition, there was evidence of increased mitral stenosis; the mitral valve gradient was 15 mmHg and the mitral valve index 0·8 cm^2/m^2 (Table). At this time, echocardiography indicated distinct systolic anterior motion of the anterior mitral leaflet, with prolonged contact between the anterior mitral leaflet and ventricular septum (Fig. 1). Because of the patient's persistent symptoms, evidence of residual left ventricular outflow tract obstruction, increasing mitral valve gradient, and diminished valve area, it was thought that she would benefit from mitral valve replacement. Hence, a no. 25 Björk-Shiley prosthesis was inserted on 15 May 1975. The excised mitral valve was diffusely fibrotic, non-calcified, and showed fused commissures. Immediately after operation a maximum peak systolic gradient of 25 mmHg was recorded between left ventricle and aorta in the

Table *Haemodynamic data*

	Case 1					*Case 2*
Date	*8/10/74*	*16/10/74*	*12/5/75*	*15/5/75*	*23/5/75*	
Pressures (mmHg)						
Right ventricle	45/3	Aortic valve replacement	40/6	Mitral valve replacement	Death	26/10
Pulmonary artery	45/20(25)		40/20(28)			32/15(22)
Pulmonary capillary wedge	17		20			13
Left ventricle	240/14		240/18			185/22
Systemic artery	160/50		160/75			125/65
Left ventricular peak systolic gradient	80*		80†			60‡
Mean diastolic mitral valve gradient	5		15			—
Indices						
Aortic valve index (cm^2/m^2)	0·2		—			—
Mitral valve index (cm^2/m^2)	1·8		0·8			—
Cardiac index (l/min per m^2)	2·3		2·2			3·4

Symbols:
*Across aortic valve as shown by pullback pressure recording from left ventricle to aorta.
— = Data not available.
†Obtained by simultaneous recording from left ventricle and femoral artery.
‡30 mmHg aortic valvular gradient and 30 mmHg subaortic gradient.

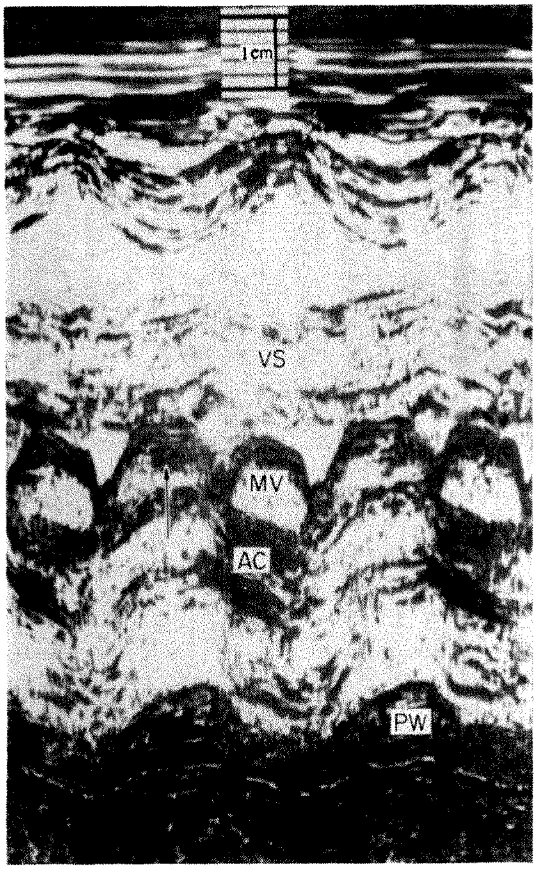

Fig. 1 *Echocardiogram recorded in case 1 under basal conditions 7 months after aortic valve replacement, when a residual 80 mmHg gradient was present between the left ventricle and femoral artery. Distinct systolic anterior motion of the anterior mitral leaflet is shown (arrow). MV, mitral valve; VS, ventricular septum; PW, posterobasal left ventricular free wall; AC, mitral annular calcification.*

operating room. Postoperatively she had a low output state with shock and impaired renal function, and died 8 days after operation.

At necropsy the heart was increased in weight (500 g). All 4 cardiac chambers were normal in size. Maximal ventricular septal thickness was 24 mm, posterobasal left ventricular wall thickness was 21 mm, and septal-free wall ratio was 1·1. There was no endocardial contact plaque on the ventricular septum. The mitral annulus was heavily calcified. Both the aortic and mitral prostheses were free of thrombus and the poppets moved freely. The coronary arteries were free of significant luminal narrowing.

Histological examination of the ventricular septal and left ventricular free wall myocardium showed the vast majority of cardiac muscle cells to be in normal parallel alignment. Small foci of disorganised cardiac muscle cells (Teare, 1958; Ferrans *et al.*, 1972; Maron *et al.*, 1974) were present in the vencular septum (totalling only 0·7% of the area occupied by cells cut longitudinally) and were more limited in extent than those usually found in patients with hypertrophic cardiomyopathy (Maron *et al.*, 1978). Echocardiographic studies performed in the patient's three first degree relatives (2 sons and a sister) revealed a normal septal-free wall ratio in each.

Case 2

A 40-year-old woman was first recognised as having coarctation of the aorta as an adolescent. This malformation was repaired at age 21. The patient was in good health until age 39 when she noted exertional dyspnoea, fatigue, occasional paroxysmal nocturnal dyspnoea, and angina pectoris. When admitted to hospital, she was in functional class II to III. On examination, she had a grade 3/6 systolic ejection murmer along the left sternal border which increased with the Valsalva manoeuvre and diminished with squatting. Systemic blood pressure was 135/90 mmHg. Electrocardiogram showed flattened T waves in leads III, aVF, and V4 to V6. Chest radiograph showed normal heart size (cardiothoracic ratio = 0·47). On the echocardiogram ventricular septal thickness was 18 mm, posterobasal left ventricular free wall thickness was 10 mm, and septal-free ratio was 1·8 (Fig. 2). Left ventricular transverse internal dimension in diastole was normal (51 mm), left atrial transverse dimension was slightly increased (43 mm), and aortic root diameter was normal (26 mm). The mitral valve was positioned anteriorly in the left ventricular cavity, as evidenced by a mitral valve position index of 0·6 (Henry *et al.*, 1975). Mild systolic anterior motion of the anterior mitral leaflet was present. Echocardiographic studies were also performed in the patient's 7 first degree relatives (2 sibs and 5 offspring); normal septal-free wall ratio was present in each.

Haemodynamic data from the patient's cardiac catheterisation are summarised in the Table. A peak systolic pressure gradient of 30 mmHg was present across the aortic valve and an additional 30 mmHg gradient was present across the left ventricular outflow tract below the valve; with isoprenaline infusion the overall gradient increased to 85 mmHg. Left ventricular angiography showed obvious cavity obliteration in end-systole and a mildly thickened aortic valve; no mitral regurgitation was present. Coronary arteriography showed normal arteries.

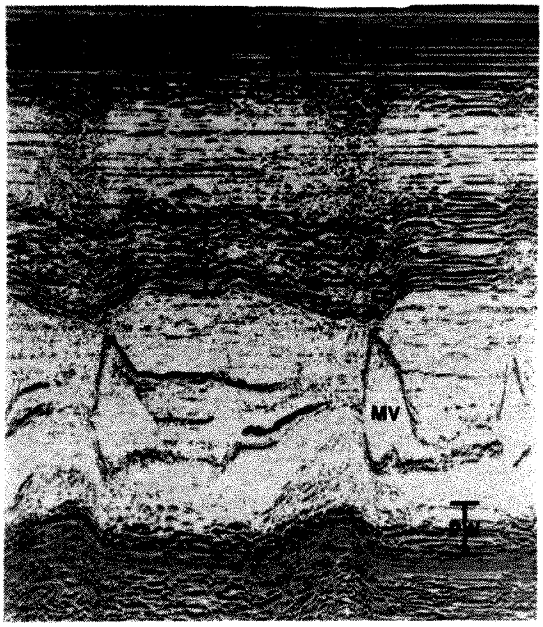

Fig. 2 *Echocardiogram recorded in case 2 showing disproportionate thickening of the ventricular septum (VS) with respect to the posterobasal left ventricular free wall (PW). At a level inferior to that shown here, ventricular septal thickness was slightly greater (18 mm) but posterobasal left ventricular free wall thickness was not significantly different. This study was obtained at a time when the patient was taking propranolol and, hence, systolic anterior motion of the anterior mitral valve was not present.*

Discussion

Disproportionate septal thickening present in the 2 patients reported here appeared to be secondary to underlying cardiac diseases (Maron *et al.*, 1977a) rather than to genetically transmitted hypertrophic cardiomyopathy. This conclusion was suggested by the following evidence: (1) echocardiographic studies in 10 first degree relatives of both patients showed normal septal-free wall ratios; and (2) the arrangement of cardiac muscle cells in ventricular septal myocardium obtained at necropsy from case 1 was not typical of hypertrophic cardiomyopathy (Teare, 1958; Ferrans *et al.*, 1972; Maron *et al.*, 1974, 1978), that is, numerous disorganised cardiac muscle cells were not present. It is probable that disproportionate septal thickening was secondary to the haemodynamic consequences of severe aortic and mitral valvular stenosis in case 1 and of coarctation of the aorta (repaired at age 21) and mild aortic valvular stenosis in case 2.

Hence, the left ventricular outflow obstruction and systolic anterior motion of the anterior mitral leaflet present in our 2 patients shows that these abnormalities may occasionally be associated with the secondary form of disproportionate septal thickening that can be found in some patients with acquired or congenital heart disease. In case 1 the pronounced systolic anterior motion of the anterior mitral leaflet demonstrated echocardiographically was associated with a large residual systolic pressure gradient between left ventricle and systemic artery after aortic valve replacement. Since there was no evidence at necropsy of significant obstruction produced by the aortic prosthesis, it appears reasonable to conclude that the gradient was caused by mitral-septal apposition. In case 2 the mild degree of systolic anterior motion of the anterior mitral leaflet present was consistent with the small subaortic gradient recorded at cardiac catheterisation.

In case 1 the apparent discrepancy between necropsy and echocardiographic assessments of septal-free wall ratio has been explained in a previous study (Maron *et al.*, 1977b). In brief, in patients with disproportionate septal thickening the left ventricular free wall thickens considerably more than the ventricular septum in systole. Since postmortem hearts are often fixed in the systolic phase of the cardiac cycle, septal-free wall ratios obtained at necropsy, or in systole by echocardiography, are usually smaller than ratios obtained in diastole by echocardiography (as per convention).

Another interesting point regarding case 1 is that systolic anterior motion of the anterior mitral leaflet occurred despite the presence of organic mitral stenosis. The ability of the mitral valve to move into the left ventricular outflow tract and abut against the ventricular septum during systole can probably only occur in patients with mitral stenosis in which the mitral valve leaflets are not calcified and manifest a considerable degree of mobility.

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Atrial infarction leading to rupture

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SUMMARY In the case described, necrosis of the atrial musculature led to rupture of the chamber. This was overlooked for 4 days until the patient died of ventricular rupture. This unusual complication of atrial infarction may be amenable to surgical repair if recognised in time.

The high gain recording of P waves in the presence of AV block made it possible to evaluate the P wave changes during atrial infarction: (1) changes in the configuration and width of the P wave, probably resulting from intra-atrial conduction defect; (2) depression of the PR segment (0·04 to 0·07 mV); and (3) a previously unrecorded convexity in the first portion of the PR segment, in the leads in which the depression of the PR segment was observed.

Atrial infarction is a poorly defined and rarely recognised entity. Its clinical diagnosis is masked by the usually concomitant ventricular infarction, whereas the electrocardiographic diagnosis is based on vague signs such as 'abnormal displacement of the PR segment' or 'abnormal P wave configuration' (Wilson and Knudson, 1954; Freundlich and Sereno, 1959; Liu *et al.*, 1961; Flowers and Horan, 1966; Sivertssen *et al.*, 1973). Pathological diagnosis is also difficult and made only after careful search in the atrial musculature (Cushing *et al.*, 1942; Soderstrom, 1948; Wartman and Hellerstein, 1948; Liu *et al.*, 1961; Sivertssen *et al.*, 1973).

However, clinical and experimental studies show that atrial infarction influences the clinical course of myocardial infarction, leading to supraventricular arrhythmias, mural thrombi, and far less commonly the rupture of the chamber (Abramson *et al.*, 1938; Kohn *et al.*, 1954; James, 1961; Liu *et al.*, 1961; Levine *et al.*, 1972; Sivertssen *et al.*, 1973; Cristal *et al.*, 1975).

The purpose of this report is to describe a case in which the diagnosis of atrial infarction was made before death, with the aid of a method that allows the high gain recording of P waves (Cristal and Freidberg, 1974). The occurrence of atrial rupture was overlooked until necropsy examination.

Case report

A 71-year-old woman was admitted to the coronary care unit on 11 June 1974, complaining of epigastric pain, cold sweating, and recurrent vomiting of 4 hours' duration. Three similar but shorter episodes had occurred during the previous month. She had been known to suffer from arterial hypertension for the past five years, but had received no treatment.

On admission, her blood pressure was 200/110 mmHg. No other abnormal findings were noted upon physical examination. The electrocardiogram showed signs of acute inferior wall myocardial infarction. A significant rise in serum levels of cardiac enzymes confirmed the diagnosis of myocardial necrosis. The chest *x*-ray film was normal.

On the third day in hospital, a variable degree of AV block developed. The heart rate ranged from 40 to 60 beats per minute and responded satisfactorily to intravenous administration of atropine. The atriogram, described below, showed signs of atrial infarction.

On the sixth day, the patient's condition deteriorated while the heart rate remained unchanged (40-60 beats/minute). She became confused and incontinent of urine. The blood pressure fell to 130/70 mmHg and the venous pressure rose for the first time. During an attempt to place a temporary pacemaker through the right subclavian vein, the patient became restless and uncooperative, and cried out; the procedure had to be stopped before the electrode reached the right atrium. Immediately afterwards, the blood pressure dropped to 70/50 mmHg but rose spontaneously to 110/70 mmHg.

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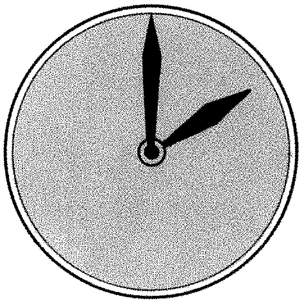

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A chest *x*-ray film showed widening of the upper mediastinum on the right side, not seen previously and attributed to intramediastinal haemorrhage, probably caused by tearing of the subclavian vein. The haemoglobin dropped from 13·0 to 9·5 g/dl and the patient received 2 units of packed cells. Her condition remained stable for the next 3 days, despite an episode of praecordial pain with electrocardiographic confirmation of extension of the infarction to the lateral wall on the seventh day.

On the ninth day she complained of praecordial pain and dyspnoea. She suddenly lost consciousness and the blood pressure dropped to zero, while her heart rate was stable (80 beats/minute). She was treated with oxygen, digoxin, glucagon, and fluids, and gradually her blood pressure rose to 100/70 mmHg. She regained consciousness and passed 300 ml urine within a one-hour period. Venous angiography was performed and, with the diagnosis of perforation of the subclavian vein, the patient was transferred to the operating room. At operation no mediastinal haemorrhage was found, but there was a large amount of blood in the pericardium. While opening the pericardium, there was a sudden massive haemorrhage of at least 3 litres and the patient went into cardiac arrest. Two tears were noted in the myocardium: one in the inferior wall of the left ventricle and the other in the posterior wall of the right atrium. The patient received 8 units of blood under pressure. All attempts to suture the ventricular rupture failed and the patient died on the operating table.

NECROPSY FINDINGS

At necropsy the heart weighed 400 g. Numerous focal haemorrhages were seen on the anterior and posterior walls of the left ventricle, the posterior wall of the left atrium near the interatrial septum, and on the posterior wall of the right atrium. A complete rupture of the myocardium, 4·5 cm long, was seen in the posterior wall of the left ventricle near the interventricular septum. Another rupture, 1·5 cm long, was seen in the posterior part of the interatrial septum, extending to the posterior wall of the right atrium. In the proximal part of the right coronary artery there was an organised thrombus with recanalisation.

Histological sections from both atria showed foci of myocardial infarction in the posterior wall of the right atrium, the left atrium, and the interatrial septum; infarction 7 to 8 days old and more recent infarction (3 to 4 days old) were seen. Histological sections from the posterior wall of the left ventricle also showed foci of infarctions, 7 to 8 days old, 3 to 4 days old, and 24 to 28 hours old.

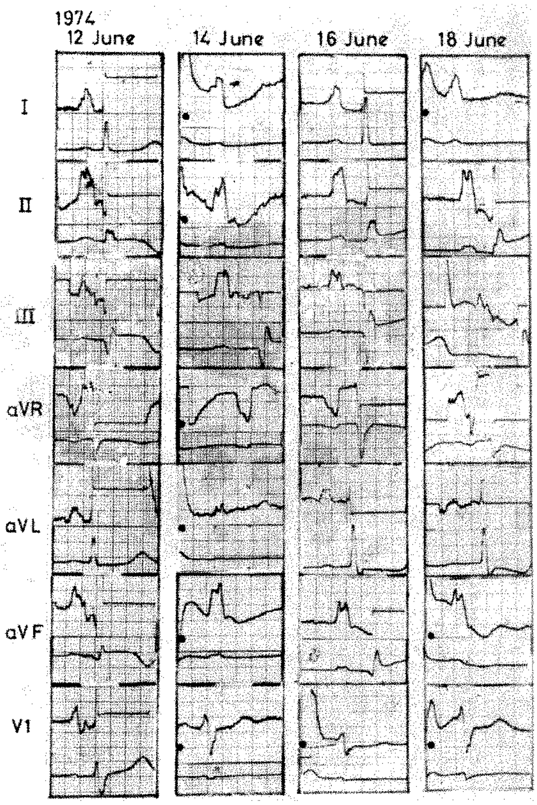

Fig. *Four consecutive atriograms—see text.*

COMMENTS ON ATRIOGRAMS

The atriogram shows P waves enlarged tenfold, recorded simultaneously with the standard electrocardiogram at a paper speed of 50 mm/s (Cristal and Freidberg, 1974). The Figure shows four consecutive tracings and the most important measurements of the atriograms are shown in the Table. Atrial infarction was thought to be present because of

Table *Measurement of some relevant features in the atriograms*

Date	*P wave width (ms)*	*Components*			*PR depression (mm)*	*PT_a* (atrial depolarisation) (ms)*
		1st (ms)	*2nd (ms)*	*3rd (ms)*		
12.6.74	120	45	35	40	4 (II, aVF)	—
14.6.74	105	45	20	40	—	380
16.6.74	105	45	20	40	—	340
18.6.74	115	50	30	35	5 (II, III, V1) 7 (aVF)	400

*PT_a was measured in isolated P waves during AV block.

changes in the shape and width of the P wave, changing displacement of the PR segment in leads II, III, and aVF, and the development of a convexity in the PR segment in the same leads.

(a) Changes in shape and width of the P wave were present and mainly related to the appearance and disappearance of a deflection in its middle portion.

(b) Depression of the J point (the junction between the end of the P wave and the take-off of the PR segment) was present in the atriogram of 12 June 1974 in leads II and aVF; this depression returned towards the isoelectric line during the following days, but reappeared 6 days later.

(c) A convexity was recorded in the first part of the PR segment in leads where the J point was depressed (more clearly visible during the recording of isolated P waves on 14 June 1977). This convexity, with its mirror-image in aVR, evolved progressively in the leads where it was present.

Discussion

The diagnosis of atrial infarction is based largely on the electrocardiogram. The diagnostic features agreed by all authors (Wilson and Knudson, 1954; Freundlich and Sereno, 1959; Liu *et al.*, 1961; Flowers and Horan, 1966; Sivertssen *et al.*, 1973), are the abnormal configuration of the P wave and the displacement of the PR segment. More precise criteria relating to the extent, direction, and duration of the electrocardiographic changes have not been defined and, not infrequently, recognition of atrial infarction on the standard electrocardiogram depends upon the sharp eyes of an experienced cardiologist.

In the present case, the tenfold magnification of the P waves and the fortuitous occurrence of complete AV block enabled us to study more closely the change during depolarisation and repolarisation of the atria in the course of an anatomically-proven infarction of the atrial chambers. The changes in the configuration of the P wave were transient, as in other reported cases (Liu *et al.*, 1961; Sivertssen *et al.*, 1973). We can therefore assume that atrial infarction does not necessarily change the P wave by producing a stable 'wave of necrosis' like the Q wave of the ventricular infarction, but rather it changes its configuration by altering the spread of depolarisation. Displacement of the PR segment is thought to be a crucial sign in the diagnosis of atrial infarction (Liu *et al.*, 1961; Sivertssen *et al.*, 1973) and depression of the J point is far more frequent than its elevation (Sivertssen *et al.*, 1973). In the present case, a depression of 0·04 mV was present in the first atriogram in leads II and aVF, returned toward the isoelectric line on the next atriogram, and reappeared on the atriogram recorded 6 days later. The occurrence of two separate ischaemic events within the atria was confirmed by the pathological findings. The presence of a convexity in the first part of the PR segment has never been previously described, and we are inclined to believe that this is an abnormal finding, since the normal atrial repolarisation vector must be in the opposite direction to the depolarisation vector. It is possible that this convexity is the equivalent of the ST elevation characteristic of ventricular infarction.

In retrospect, it seems likely that the infarcted right atrium ruptured 4 days before the ventricular rupture, during the unsuccessful attempt to insert an electrode through the right subclavian vein. The rise in the right atrial pressure which developed during the procedure, when the patient in the Trendelenburg position became distressed and cried, was probably an important contributing factor to the rupture. The bleeding into the pericardial sac during the first hours led to a drop in blood pressure and haemoglobin, but, later, increased intrapericardial pressure resulted in a decrease or even cessation of the bleeding. The clinical condition of the patient then remained stable for the next 5 days, until she became shocked after ventricular rupture.

Ventricular rupture is the cause of death in 8 to 11 per cent (Meurs *et al.*, 1970; Biörck *et al.*, 1972; Van Tassel and Edwards, 1972) of patients dying of myocardial infarction. By contrast, rupture of the atrial chambers is a rare complication of myocardial infarction and since the case reported by Kohn *et al.* (1954), we found no further instance reported in the publications available to us. Of the 79 cases of atrial rupture collected at that time, 15 per cent survived more than 24 hours; the authors attributed this to the fact that the bleeding into the pericardium was not as massive as in ventricular rupture. In this series, the diagnosis was never made before death. The concurrent development of atrial and ventricular rupture has never been reported before, but the occurrence of more than one ventricular rupture in the same patient has been noted in a few cases who survived the first rupture (Biörck *et al.*, 1972).

Atrial infarction is an overlooked entity and further studies are necessary in order to define more reliable criteria for its diagnosis. The recording of high gain P waves during myocardial infarction should contribute to this. In the present report, we draw attention again to the occurrence of this unusual complication of myocardial infarction and stress the fact that a patient with atrial rupture can survive long enough for it to be possible to attempt

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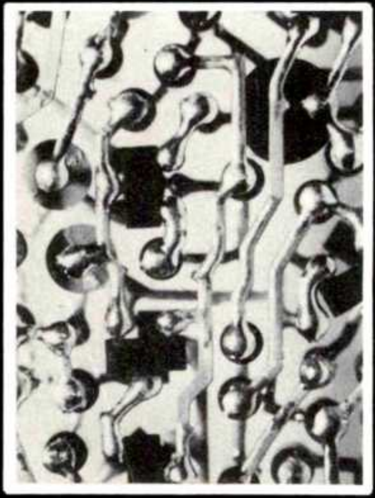

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surgical repair, provided that the diagnosis can be established.

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Requests for reprints to Dr N. Cristal, Coronary Care Unit, Soroka Medical Center, Beer-Sheba, Israel.

British Heart Journal, 1979, **41**, 354-355

Pulsus alternans induced by glyceryl trinitrate paste in a patient with alcoholic cardiomyopathy

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From the Division of Cardiology, University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma, USA

SUMMARY Application of a small dose of glyceryl trinitrate paste (0·25 in) resulted in severe left ventricular dysfunction with the appearance of pulsus alternans in a patient with alcoholic cardiomyopathy. The echocardiogram showed a reduction in the amplitude and velocity of motion of the left ventricular posterior wall on alternate beats. Leg elevation promptly reversed the pulsus alternans, and the echocardiographic abnormality. Glyceryl trinitrate paste should be used with caution and under close supervision in patients with liver dysfunction.

Reduction of afterload by vasodilator therapy has been shown to be an effective means of treating refractory cardiac failure (Mikulic *et al.*, 1975; Kovick *et al.*, 1976; Mantle *et al.*, 1976). Glyceryl trinitrate paste has a prolonged duration of action and has been shown to be a useful agent in the treatment of heart failure (Reichek *et al.*, 1974; Taylor *et al.*, 1976). Because of the widespread use of this agent it is important to recognise its possible adverse effects (Come and Pitt, 1976). This report describes a patient with alcoholic cardiomyopathy in whom an acute deterioration of left ventricular function was observed after the application of a small dose of glyceryl trinitrate.

Case report

A 34-year-old white man was admitted with complaints of dyspnoea and swelling of his legs. He admitted to having consumed ½ to 1 pint of vodka each day or similar hard liquor for over 8 years. On examination, he was orthopnoeic, and had bilateral ankle oedema. His jugular venous pressure was raised 10 cm above the sternal angle at 45°. The blood pressure was 104/88 mmHg and his pulse was 124/minute and regular. The maximum impulse was in the sixth intercostal space in the anterior axillary line. There was a loud S_3 gallop. Basal râles were present. The liver was palpable 10 cm below the right costal margin and was tender. The span of the liver was 16 cm by percussion. The spleen was not palpable. The neurological examination was within normal limits.

The electrocardiogram showed left ventricular hypertrophy, and nonspecific ST-T changes. His chest *x*-ray film showed pronounced cardiomegaly and changes consistent with pulmonary oedema. The echocardiogram disclosed conspicuous ventricular dilatation (left ventricular end-diastolic dimension = 7 cm) with poor wall motion. The left atrium was enlarged. The serum electrolytes were normal. The total bilirubin was 54·7 μmol/l (3·2 mg/100 ml); direct bilirubin 32·5 μmol/l (1·9 mg/100 ml); alkaline phosphatase, 160 mU/ml (normal range 30 to 115 mU/ml); LDH, 375 mU/ml (normal range 100 to 225 mU/ml); aspartate aminotransferase (AST; SGOT), 207 mU/ml (normal range 7·5 to 60 mU/ml; CK, 74 IU/l (normal range 50 to 180 IU/l); the prothrombin time was 14·2 with a control of 10·9 seconds. The liver function tests done after control of cardiac failure were as follows: AST(SGOT) 247 mU/100 ml, serum alkaline phosphatase 151 mU/100 ml, LDH, 298 mU/100 ml, total bilirubin 27·4 μmol/l (1·6 mg/100 ml), direct bilirubin 17·1 μmol/l (1·0 mg/100 ml), and prothrombin time 16·4 seconds (control, 10·0).

His congestive cardiac failure responded well to salt restriction, digitalis, and diuretics. He was discharged on the above medications and advised to refrain from alcohol. He was seen in the outpatient clinic two months later. Though symptomatically improved he continued to have shortness of breath on exertion and his chest *x*-ray film showed pulmonary venous congestion. A trial of therapy with glyceryl trinitrate paste was, therefore, advised.

His resting blood pressure was 100/80 mmHg and his pulse was 103/minute. He was seated in bed with his head tilted up 45°. One quarter inch (0·25 in) of glyceryl trinitrate paste was applied over a 6″ × 6″ area of skin over the abdomen, covered with saran wrap, and taped on all four sides. Pulse and blood pressure were recorded every 15 minutes. Thirty minutes after the application of glyceryl trinitrate a sharp fall in the blood pressure to 74/60 mmHg was observed. His pulse was 120/minute with a distinct pulsus alternans, every other beat being barely palpable. The systolic blood pressure of the strong beat was 74 mmHg and that of the weak beat was 38 mmHg. The patient did not feel dizzy and had not noticed any other symptoms. An echocardiogram taken at that time showed that the amplitude and velocity of left ventricular posterior wall motion was much reduced on every other beat. The carotid pulse showed a striking reduction of amplitude of every other beat, corresponding to the weak beats on the posterior wall echocardiogram. The patient was laid flat, his legs raised, and the glyceryl trinitrate paste removed. The blood pressure increased to 104/76 mmHg a few seconds after leg elevation and the pulsus alternans disappeared. The echocardiogram done at this time showed regular left ventricular posterior wall contractions. The carotid pulse showed a disappearance of the alternans pattern. After 40 minutes the standing blood pressure was 104/64 mmHg.

Discussion

This patient clearly showed a deterioration of left ventricular function as evidenced by the development of pulsus alternans after the application of glyceryl trinitrate paste. It is interesting to speculate why this occurred. Our patient had evidence of liver dysfunction on admission. This could have been caused by alcoholic hepatitis or passive venous congestion of the liver. Though improvement in the liver function tests was noted after treatment of his failure, some tests remained abnormal. This suggested some degree of underlying liver disease. Patients with liver disease and alcoholism have cutaneous vasodilatation which may facilitate the absorption of glyceryl trinitrate paste. Our patient did show conspicuous cutaneous vasodilatation as evidenced by a very plethoric skin. Furthermore, in the presence of liver disease glyceryl trinitrate is probably not inactivated as rapidly as in the normal subject. Rapid cutaneous absorption and reduced rate of inactivation probably resulted in high blood levels of glyceryl trinitrate in our patient. This probably caused much arteriolar and venous dilatation, with a consequent fall in the blood pressure and cardiac output. The heart rate increased from 103 to 120 beats per minute. These factors probably resulted in pulsus alternans. The echocardiogram clearly showed a reduction in amplitude and velocity of motion of the left ventricular posterior wall on alternate beats. This abnormality disappeared after leg elevation.

One may argue that he had a low left atrial pressure before treatment with glyceryl trinitrate. The presence of pulmonary venous congestion on the chest *x*-ray film taken on the day of application of glyceryl trinitrate paste precludes such an argument. Thus, his left ventricular filling pressure was probably high before the treatment. The small amount of glyceryl trinitrate was sufficient to produce severe venous dilatation and consequent reduction of preload to place him in the steep ascending limb of the Starling curve, with a resultant fall in cardiac output.

It is of interest that his hypotension and pulsus alternans were promptly corrected by leg elevation. This suggests that his hypotension and left ventricular dysfunction (manifested as pulsus alternans) were the direct result of pronounced venous pooling which produced a drastic reduction in preload. It is noteworthy that the patient remained asymptomatic in spite of considerable haemodynamic deterioration.

We conclude that the dose of glyceryl trinitrate paste should be carefully adjusted in patients with hepatic dysfunction. Monitoring of blood pressure, heart rate, and echocardiographic left ventricular wall motion may be effective in avoiding serious sequelae.

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Requests for reprints to Dr P. A. N. Chandraratna, Division of Cardiology, S-10, Veterans Administration Hospital, 5901 East Seventh Street, Long Beach, California 90822, USA.

British Heart Journal, 1979, **41**, 356-359

Echocardiographic identification of aorta and main pulmonary artery in complete transposition

Sir,

A. B. Houston and his colleagues have shown two-dimensional echocardiographic findings on the spatial relation between the great arteries (*British Heart Journal* (1978), **40**, 377). We have applied a similar procedure routinely to our complicated heart anomalies and defined 3 transverse planes as follows (Satomi *et al.*, 1978).

Plane 1 is where the echo of the semilunar valve of the posterior great artery is obtained. Plane 2 is slightly more cephalad in direction, where the echo of the semilunar valve of the anterior great artery is seen. Plane 3 is more cephalad still, where neither semilunar valve is seen.

When the interrelation of the great arteries is spiral, an anteriorly positioned artery at plane 1 runs beside and behind the other artery and the posterior wall echo of the anterior artery extends posteriorly at plane 3 (Fig. 1a). When parallel, its parallel interrelation of the echo images from the great arteries is maintained in the 3 transverse planes or the posterior wall echo of the posterior great artery may extend posteriorly, or give off a branching image (Fig. 1b).

The artery showing the posterior extension or branching is the pulmonary artery which is confirmed by contrast two-dimensional echocardiogram (Fig. 2), though it has not been illustrated by Houston *et al.*

We have made correct anatomical diagnoses not only in many cases of complete transposition but also in those with double outlet right ventricle or corrected transposition of the great arteries showing parallel interrelation. This procedure has been very useful in the diagnosis of congenital heart disease as Dr Houston and his colleagues have commented.

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Yukio Komatsu, and
Atsuyoshi Takao,
The Heart Institute Japan,
Tokyo Women's Medical College,
10 Kawada-cho, Shinjuku-ku,
Tokyo 162, Japan.

Reference

Satomi, G., Shimizu, K., Komatsu, Y., and Takao, A. (1978). Two dimensional echocardiographic diagnosis of congenital heart disease. Part 1: Spatial interrelationship between the great arteries. *Journal of Cardiography*, in the press.

This letter was shown to Dr Houston and his co-authors who reply as follows:

Sir,

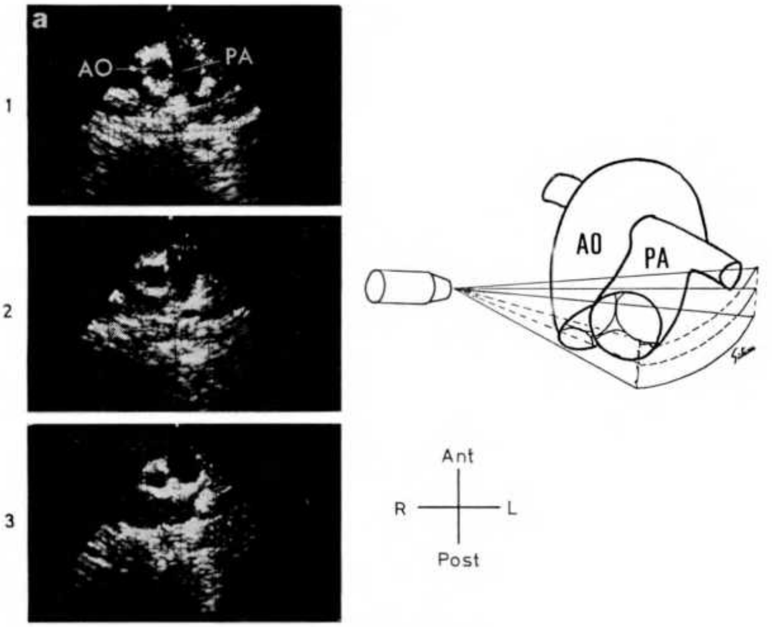
We agree with Dr Satomi's comments.

In patients with parallel great arteries the 3 scanning planes he describes correspond to the manoeuvre we use to attempt to demonstrate branching of the main pulmonary artery described in the discussion as 'tilting or edging the scanning plane upwards'. In an earlier study of older patients with transposition (Houston *et al.*, 1977) we reported that it was not always possible to see both semilunar valves in a single scanning plane. We have subsequently found that with the more oblique high transverse plane, both valves are occasionally not recorded simultaneously in subjects with normally (spirally) related great arteries. In our studies of patients with other great artery anomalies we have found that in all infants the longitudinal view allows the great arteries to be rapidly identified while it is not always possible to identify clearly the bifurcation of the pulmonary artery. The posterior extension of the pulmonary artery described by Dr Satomi and shown in our Fig. 2 represents the posterior turn of the pulmonary artery at a lower level than the aorta which still appears as an approximately circular echo-free space.

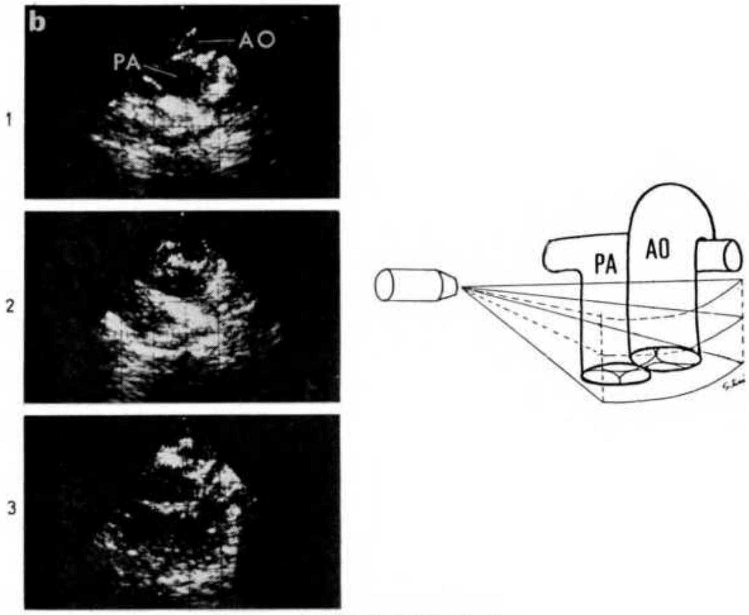
A. B. Houston,
N. L. Gregory, and
E. N. Coleman,
Royal Hospital for Sick Children,
Yorkhill, Glasgow.

Reference

Houston, A. B., Gregory, N. L., and Coleman, E. N. (1977). Two-dimensional sector scanner echocardiography in cyanotic congenital heart disease. *British Heart Journal*, **39**, 1076-1081.



ASD (S,D,N) spiral



1-TGA (S,L,L) parallel

Fig. 1

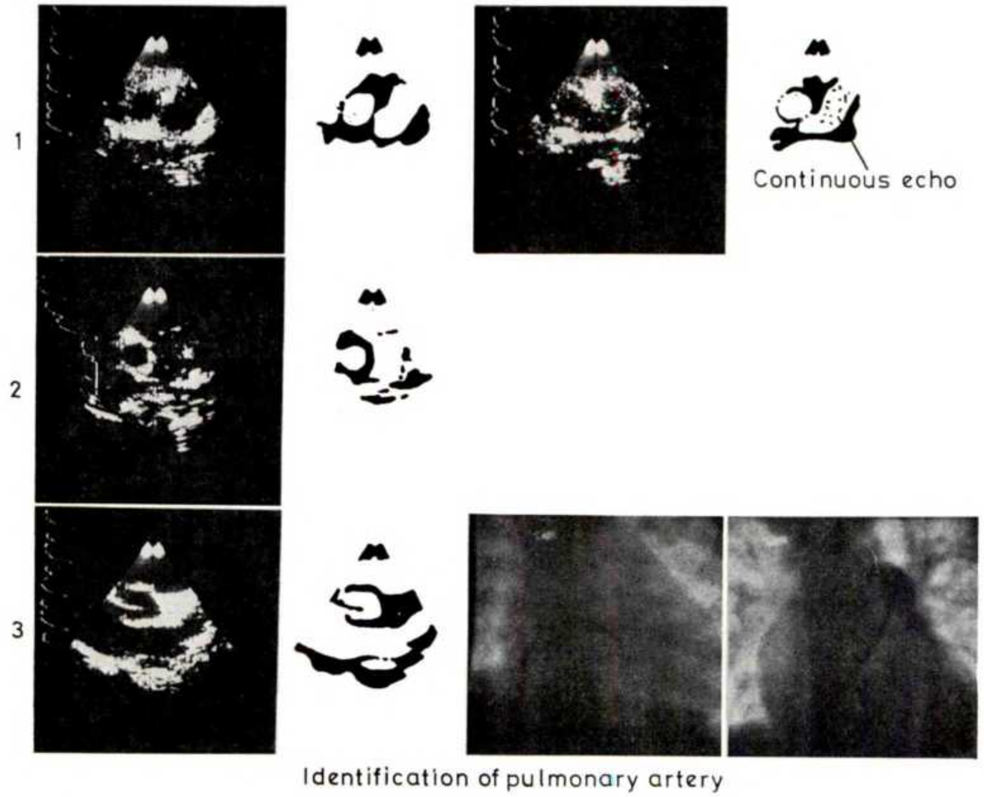


Fig. 2

Echocardiographic visualisation of the interatrial baffle after Mustard's operation

Sir,

We read with great interest the communication by Hunter *et al.* (*British Heart Journal* (1977), **39**, 954). The authors described thickening and diminished movement of the baffle in 4 patients with caval obstruction.

We recently saw a patient with baffle obstruction who, in addition, had a baffle leak and pronounced systolic anterior movement of the tricuspid valve on M-mode echocardiogram (Fig.). Cardiac catheterisation showed an opening in the baffle suture line, a 1·3:1 Qp/Qs ratio, an 11 mmHg mean pressure gradient between the superior vena cava and the systemic venous atrium, and diffuse right ventricular hypokinesis. There was no right ventricular outflow tract obstruction.

The echocardiographic finding of tricuspid valve systolic anterior motion after Mustard operation has not been reported previously. Nanda *et al.* (1976) however described systolic anterior motion of the baffle itself in 3 patients who had a 2:1 or greater baffle shunt. Because both the baffle obstruction and shunt were localised to an area low in the systemic venous chamber in our patient, the stream may have impinged on the tricuspid valve, causing it to move anteriorly during systole. Alternatively, the abnormal tricuspid valve motion may relate to the right ventricular dysfunction.

Evlin Kinney, William Reeves,
William Berman, Jun, and Robert Zelis,
The Milton S. Hershey Medical Center,
The Pennsylvania State University,
Hershey, Pennsylvania 17033, USA.

Reference

Nanda, N. C., Gramiak, R., Stewart, S., and Manning, J. (1976). Echocardiographic recognition of intra-atrial baffle dysfunction. In *Ultrasound in Medicine*, Vol. 2, pp.13-20, ed Denis White and Ralph Barnes. Plenum Press, New York.

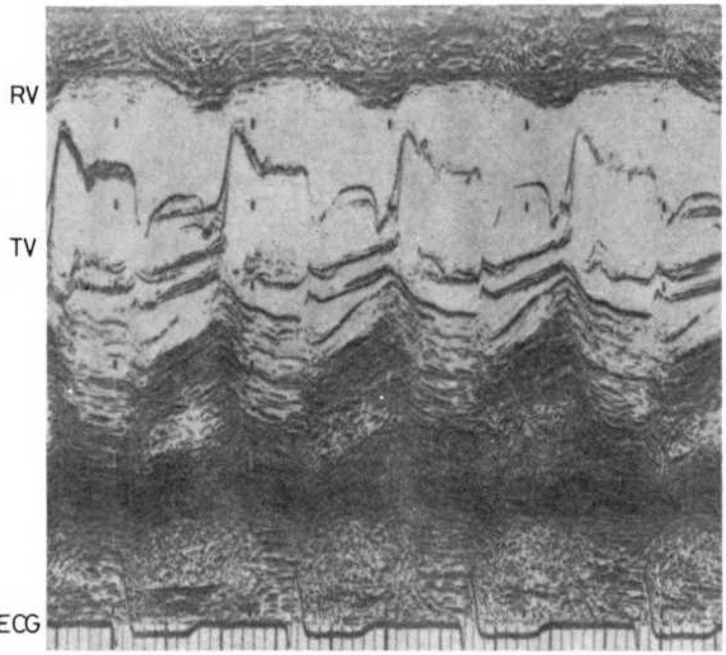


Fig. *M-mode echocardiogram showing prominent systolic anterior motion of the tricuspid valve. RV, right ventricle; TV, tricuspid valve.*

British Heart Journal, 1979, **41**, 360-384

Proceedings of the British Cardiac Society

THE AUTUMN MEETING of the British Cardiac Society was held at the Wembley Conference Centre on Monday and Tuesday, 20 and 21 November 1978. The President, W. SOMERVILLE, took the Chair during private business. At the scientific sessions the Chair was taken by J. F. PANTRIDGE.

Abstracts of Papers

Young Research Workers Award 1978

Functional significance of coronary collateral circulation during dynamic exercise evaluated by thallium-201 myocardial scintigraphy

Ray Wainwright
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Sixty-five patients with documented coronary artery disease were investigated by thallium-201 (^{201}Tl) scintigraphy to determine the role of the collateral circulation during exercise. Fifty-three patients had complete proximal occlusion of at least 1 major coronary artery. One patient had total occlusion of all 3 coronary arteries. Sixty-four collateral channels were identified, graded, and compared with corresponding regions of the myocardial scintigram. Tracer uptake was also graded and classified as various degrees of protection from ischaemia.

A significant correlation between good collaterals with complete protection and poor or absent with no protection was noted ($P < 0{\cdot}0005$, coefficient of contingency = 0·50).

Seventeen patients (20 occluded vessels) had total coronary occlusion without myocardial infarction. Collaterals conferred protection in 9/15 occlusions whereas no protection was seen in 5 occlusions without collaterals ($P = 0{\cdot}03$).

There was no difference in the protective role of homocoronary and heterocoronary collateral vessels. Hypertrophy of the first septal left anterior descending (LAD) perforator conferred significant protection in contrast to bridging collaterals and ghosting.

Evidence is presented to show that during exercise the right coronary bed in comparison to the LAD coronary bed is always preferentially protected from ischaemia, probably reflecting the transmural driving gradient between left and right ventricles.

Man and the pig are similar in this respect (Ramo *et al.*, 1970).

Reference

Ramo, B. W., Peter, R. H., Ratliff, N., Kong, Y., McIntosh, H. D., and Morris, J. J. (1970). The natural history of right coronary arterial occlusion in the pig. Comparison with left anterior descending arterial occlusion. *American Journal of Cardiology*, **26**, 156.

Quantitative approach to analysis of exercise thallium-201 scintigraphy: clinical evaluation

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Thallium-201 exercise scintigraphy provides a non-invasive technique in the investigation of patients with suspected coronary heart disease (CHD). To improve objectivity in analysis, a quantitative approach to the interpretation of image data was developed using a regions of interest technique. In healthy volunteers, under conditions of maximal exercise, a normal variation in inter-regional count densities (15%) was identified. Regional variation exceeding 20 per cent was accepted as abnormal and this criterion applied to the interpretation of exercise scintiscans from 50 patients with chest pain. Image data proved sensitive (91%) and specific (82%) for the detection of patients with significant CHD. However, a discrepancy between extent of disease determined by scintigraphy (50 areas of hypoperfusion) and arteriography ($\geqslant 71$ diseased vessels) was noted in patients with $\geqslant 2$ vessel disease. In 30 patients with multiple vessel disease, the influence of collateral circulation and severity of occlusion was explored. Functional capacity of collateral circulation appeared variable offering protection from ischaemia in 9 of 16 non-infarcted zones. The severity of occlusion modified tracer distribution such that areas supplied by diseased vessels may appear normal if adjacent areas were supplied by vessels with higher grade occlusion.

Thus, computer reading of exercise thallium-201 scintiscans could be applied in the diagnosis of CHD. A range of normal tracer concentration could be identified and abnormality defined. The technique was accurate in detecting patients with CHD but was limited in determining the extent of disease.

Relation between praecordial projection of ST segment changes after exercise and coronary angiography

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Stress testing has now become a standard diagnostic tool in the non-invasive evaluation of patients presenting with chest pain. The sensitivity depends largely on the lead system used and rarely exceeds 80 per cent. In addition, attempts to evaluate the site and severity of arteriographic lesions have proved to be disappointing. In this study a technique for recording praecordial areas of ST segment changes before and after exercise is described and the results compared with the findings at coronary arteriography in 109 patients. This technique showed a sensitivity of 95 per cent and specificity of 91 per cent for the detection of significant coronary artery disease. Typical praecordial projections of ST segment changes were found when the left anterior descending or right coronary artery was involved alone. In 25 per cent with single vessel disease there was an overlap in the areas of the praecordium involved. In those patients with extensive coronary artery disease widespread praecordial electrocardiographic changes were present in 64 per cent, a finding not seen when the left and right coronary arteries were involved alone.

Praecordial exercise mapping has been shown to be valuable in the diagnosis of coronary artery disease and in the identification of patients with three vessel disease.

Ventricular defibrillation

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Physiology, The Queen's University, Belfast
BT7 1NN

It is stated that one-third of adult patients cannot be defibrillated by conventional defibrillators which store 400 Joules and an energy-dose body weight related concept for defibrillation with a peak current of 1 Amp/kg has been suggested. This suggestion is contested. The mean peak current/kg required for defibrillation in the clinical situation has been measured for the first time and found to be 0·35 ± 0·05 Amp/kg. No correlation was found between body weight and mean peak current ($r = 0{\cdot}121 \pm 0{\cdot}314$).

In dogs shocks of high energy caused more myocardial damage than those of identical total energy delivered by repeated low energy shocks (30·1 ± 10·6 g for 10 shocks of 400 Joules compared with 0·5 ± 0·3 g for 40 shocks of 100 Joules). Stimulation of the autonomic nervous system did not appear to be a factor since depletion of catecholamines by reserpine (0·25 mg/kg) and blockade with propranolol (0·4 mg/kg) and atropine (0·2 mg/kg) did not reduce damage. Damage of thermal origin was unlikely since the mean temperature rise was 0·002°C ± 0·056°C after repeated shocks. It is likely that the damage from DC shock results from a direct effect on the myocardial cells.

Coarctation, tubular hypoplasia, and ductus arteriosus: a histological study

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The ductus arteriosus, coarctation, and tubular hypoplasia of the aortic arch have been studied histologically so as to determine any relation between them. Thirty-five specimens of the aortic arch including the ductus arteriosus were serially sectioned. Seven specimens were from anatomically normal hearts and 28 were from congenitally malformed hearts of which 12 were associated with coarctation and/or tubular hypoplasia. Ductal tissue was distinguished from aortic tissue as being essentially muscular and lacking the regularly spaced elastic lamellae. Specimens with coarctation and/or tubular hypoplasia showed an abnormal sling of ductal tissue around the orifice of the aortic isthmus. These cases were affected by some form of obstruction or restriction to aortic blood flow. In 6 of these a diaphragm of ductal tissue was observed to form the coarctation lesion. Since the coarctation lesion can coexist with tubular hypoplasia of the aortic arch, it is necessary to distinguish between these different forms of obstruction to blood flow through the aortic arch. The finding of a ductal 'sling' in all 12 cases with arch obstruction in the presence of reduced aortic flow is of major significance with regard to theories concerning the formation of obstructive lesions.

Development of inlet zone of right ventricle in man

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The mode of development of the inlet portion of the right ventricle is one of the most contentious topics in human embryology, with far-reaching consequences concerning the understanding and nomenclature of malformed hearts. Much disagreement is purely semantic in origin. Observations in 12 human embryos confirm that after ventricular looping the entire atrioventricular canal is committed to the proximal segment of the primary heart tube while the truncus is supported by the distal segment. The primary tube at this stage is lined with endocardial jelly and devoid of trabeculations. Trabecular pouches derive from both segments to either side of the ventricular constriction, the pouch derived from the inlet segment becoming the left ventricular trabecular zone while the pouch derived from the outlet segment forming the right ventricular trabecular zone. A trabecular septum is formed between them. The atrioventricular canal is septated by the endocardial cushions, but the inferior cushion itself fuses with the trabecular septum from its inception, committing a sleeve of inlet component of the primary tube to the right ventricle. This sleeve, together with a sleeve of outlet component form the inlet portion of the definitive right ventricle. These findings show that double inlet univentricular heart of left ventricular type cannot be considered as arrested normal development, and that most disagreements concerning its morphogenesis are spurious, being alleviated by usage of descriptive terms for embryological events.

Lung biopsy in congenital heart disease: improved clinicopathological correlations

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A morphometric study of regional variation in lung structure in infants with ventricular septal defect (VSD) and pulmonary hypertension showed that one section of lung tissue, 1 cm^2, was representative of the entire pulmonary vascular bed and also gave a satisfactory assessment of lung growth. Subsequently, the lung was biopsied in 15 patients with an isolated VSD, a univentricular heart, or transposed great arteries and VSD. Lung structure was quantified using 3 age-related criteria: (i) abnormal extension of muscle into intra-acinar arteries, (ii) percentage arterial thickness, and (iii) number of intra-acinar arteries per unit area of lung, as related to alveolar number. These measured changes were related to the Heath and Edwards classification.

All showed abnormal extension of muscle. In arteries 50 to 100 μm in diameter, mean percentage medial thickness correlated significantly with mean pulmonary arterial pressure ($r = 0{\cdot}76$; $P < 0{\cdot}01$), as did the alveolar/arterial ratio ($r = 0{\cdot}71$; $P < 0{\cdot}02$). Excluding cases of univentricular heart, muscularity also correlated with pulmonary vascular resistance ($r = 0{\cdot}70$; $P < 0{\cdot}05$). Not only did the structural development correlate with the haemodynamic findings, but, in retrospect, within each diagnostic group, the combination of structural features could be related to the outcome of corrective surgery.

Lung scan abnormalities in hypertensive pulmonary vascular disease

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Perfusion and ventilation lung scans have been performed on a large field gamma camera in 7 patients with post-tricuspid shunts and the Eisenmenger syndrome and in 3 with residual pulmonary hypertension after repair of ventricular septal defect. The distribution of regional pulmonary perfusion was imaged using technetium-99m labelled albumin microspheres or macroaggregates; and of regional ventilation during constant inhalation of the short-lived isotope krypton-81m. Anterior, posterior, and 2 lateral views were obtained.

In all cases ventilation scans were normal but perfusion scans showed patchy non-segmental defects. The distribution of these defects was variable, though often more pronounced in the upper lung fields. In 2 patients with persistent ductus arteriosus defects were more prominent in the left lung. The proportion of the injected dose entering the lung was calculated in 7 patients by estimating the count rate from microspheres in the lungs and head. In all these patients there were sufficient particles in the lungs for statistical reliability. In no patients were there any side effects from systemic circulation of the albumin particles.

The pathological basis for the perfusion defects is uncertain. It is well recognised that dilatation lesions are not uniformly distributed within the lungs. Alternatively, it is possible that they result from thrombosis *in situ* in the pulmonary arterial bed.

Quantification of coronary heart disease

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Each of the 4 major epicardial coronary arteries in 106 patients with coronary heart disease was divided into 5 mm long segments and a Movat-stained histological section was prepared and examined from each segment. An average of 56 5 mm long segments was examined from each patient. Of 5387 5 mm long segments examined, 1924 (36%) were 75 to 100 per cent narrowed in cross-sectional area by atherosclerotic plaque (controls = 3%), another 36 per cent were 51 to 75 per cent narrowed (controls = 22%), 20 per cent were 26 to 50 per cent narrowed (controls = 44%), and only 9 per cent were less than 26 per cent narrowed (controls = 32%). The 22 patients with clinically isolated, *unstable angina pectoris* had the highest percentage of 5 mm long segments 76 to 100 per cent narrowed in cross-sectional area by atherosclerotic plaque, namely 48 per cent; the 26 patients with *healed myocardial infarcts* had the smallest percentage of segments 76 to 100 per cent narrowed, namely 28 per cent; the 27 patients with *acute myocardial infarction* and the 31 patients with *sudden coronary death* were intermediate (35%). Thus, the patients with the least amount of myocardial damage, that is angina pectoris, had the severest degree of coronary narrowing, and those with the severest degree of myocardial damage, that is healed myocardial infarction, had the least degree of coronary narrowing.

Multicentre prospective randomised study of coronary bypass surgery in angina pectoris. Survival at 2 years

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The patients included are men below 65 with angina pectoris, ≥ 50 per cent obstruction in at least 2 major vessels and left ventricular ejection fraction $\geq 0{\cdot}5$. Seven hundred and sixty-eight patients were randomised: 373 into a medical treatment (M) group and 395 into a surgical treatment (S) group. All medical and 394 surgical patients were available to follow up. There were no significant differences between the 2 groups regarding the distribution of baseline variables. Twenty-six patients of S-group did not receive surgery: 6 died before operation and 20 refused surgery. Fifty patients of M-group were operated on because of symptoms not responding to medical management. All these 76 patients were retained in their original treatment groups for the analysis. Operative (hospital) mortality was 3·6 per cent in all operated patients while it was 3·5 per cent in S-group patients. The only significant 2-year survival difference was found in the subset of patients with 3-vessel disease: the survival was better in the surgical group.

		No. of patients	*Survival %*	*Difference S-M ± CI %*
Total	M	373	92·5	2·2 ± 3·5
	S	394	94·7	
Left main disease	M	31	87·1	5·8 ± 15·2
	S	28	92·9	
2-vessel disease	M	154	96·7	−3·5 ± 4·9
	S	147	93·2	
3-vessel disease	M	188	89·9	6·0 ± 5·0*
	S	219	95·9	

*$P < 0{\cdot}05$; CI = 95% confidence interval.

Co-operative trial in primary prevention of ischaemic heart disease using clofibrate

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A double-blind intervention trial was conducted between 1965 and 1975 to test the hypothesis that the incidence of ischaemic heart disease (IHD) in middle-aged men can be reduced by lowering raised serum cholesterol levels. It was carried out in Edinburgh, Budapest, and Prague on 15 745 men, aged 30 to 59. The trials continued for an average of 5·3 years and comprised a high cholesterol group treated with 1·6 g clofibrate daily, a high cholesterol control group, and a low cholesterol control group. Subjects with manifest heart disease were excluded from the trial. No attempt was made to correct other risk factors for IHD.

A mean reduction of 9 per cent of the initial serum cholesterol levels was achieved in the clofibrate treated group; this was less than the 15 per cent fall expected. During treatment, serum triglyceride concentrations resembled those naturally occurring in the low cholesterol control group.

The incidence of IHD was lower by 20 per cent in the clofibrate group compared with the high cholesterol control group ($P < 0{\cdot}05$); this fall was confined to non-fatal myocardial infarcts which were reduced by 25 per cent. The incidence of fatal heart attacks was similar in the 2 high cholesterol groups and there was no significant difference in the incidence of angina. The reduction of non-fatal myocardial infarction in the clofibrate-treated group was greatest in men with the highest level and the greatest reduction in serum cholesterol.

The number of deaths, and crude mortality rates from all quarters in the clofibrate-treated group significantly exceeded those in the high cholesterol control group ($P < 0{\cdot}05$). Excluding deaths from IHD, other vascular causes, and accidents, the excess of deaths in the clofibrate-treated group compared with the high cholesterol control group was 77 compared with 47 ($P < 0{\cdot}01$). The subgroup with the greatest proportion of excess of deaths was that of conditions related to the liver, the biliary, and intestinal system. The cholecystectomy rate for gall-stones was higher in the clofibrate-treated group than in either of the control groups ($P < 0{\cdot}001$).

The results of the trial confirm the basic hypothesis that reduction of high serum cholesterol levels, even in middle-aged, can reduce the incidence of IHD. However, the excess of non-IHD and non-vascular death in the treated group and the increased incidence of gall-stones indicate that clofibrate cannot be recommended as a lipid-lowering drug for community-wide prevention of IHD.

12-lead maximal exercise testing as a predictor of severe coronary artery disease

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Seventy-two patients, average age 51 ± 9 years, underwent both maximal 12-lead treadmill testing (Bruce protocol) and coronary arteriography. Only patients with rest pain and ST segment shifts were excluded. Twenty-eight patients had normal coronary arteries, 12 had single-vessel disease ($>70\%$ luminal diameter), 14 had double-, and 14 had triple-vessel disease. Four had left main coronary disease (LMCD).

All 32 patients with 2-, 3-vessel, or LMCD had positive exercise tests while 8/12 with single-vessel disease had positive tests. Sensitivity of the 12-lead electrocardiograms during maximal stress testing was 91 per cent (cf. 75% using V5 only), with 9 per cent false negatives (25% using V5 only). Specificity and false positives were identical with both methods (86% and 14%, respectively).

The sum of ST segment shifts in all 12 leads (ΣST) was $2{\cdot}1 \pm 1{\cdot}9$ (single-vessel disease), $6{\cdot}0 \pm 2{\cdot}3$ (double-vessel disease), $9{\cdot}3 \pm 6{\cdot}5$ (triple-vessel disease), and $11{\cdot}1 \pm 2{\cdot}9$ mm (LMCD). ΣST was a significant predictor of triple-vessel and LMCD. Other significant predictors of triple-vessel and LMCD (cf. $\leq$ 2-vessel disease) were the number of electrocardiographic leads showing ischaemic changes ($6{\cdot}1 \pm 1{\cdot}8$ vs $3{\cdot}1 \pm 2{\cdot}1$, $P < 0{\cdot}001$) and the exercise stage achieved ($2{\cdot}2 \pm 0{\cdot}8$ vs $3{\cdot}3 \pm 0{\cdot}9$, $P < 0{\cdot}001$). There was a significant correlation between location of coronary artery stenoses and ischaemic areas on the exercise electrocardiogram.

It is concluded that maximal 12-lead electrocardiographic stress testing results in a higher yield of true positive tests, and can be used to predict the severity of coronary artery disease and localise areas of ischaemia.

Normalisation of electrocardiogram in survivors of myocardial infarction on beta-blockers

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The fewer the abnormalities detected on the electrocardiogram 1 to 2 years after acute myocardial infarction (AMI) the less the risk of sudden death (Leren *et al.*, 1970: coronary drug research project, 1972; Blackburn *et al.*, 1970). The effect of a beta-blocker (atenolol) on the evolution of the electrocardiogram in the chronic phase after AMI was studied in 22 patients with anterior MI. Serial 35-lead praecordial maps were performed using a reproducible technique just before discharge, 1 month after discharge, and then at 3-monthly intervals for a year.

The increase in R waves was significantly greater in the treated group as compared with the placebo group ($P < 0{\cdot}001$; Wilcoxon's rank test). The ΣR waves over 35 leads changed from an initial mean value of 62 mm (beta-blocked group) and 51 mm (placebo) (not significant) to 87·5 mm and 59 mm at 3 months ($P < 0{\cdot}1$ Student's t test); to 130 and 47 mm at 6 months ($P < 0{\cdot}001$) and to 192 and 54 mm at 1 year after MI ($P < 0{\cdot}001$). The Σ (QS) waves also showed a significant decrease in the treated group ($P < 0{\cdot}05$).

Compensatory hypertrophy and intraventricular conduction defects were excluded as possible mechanisms of increase in R waves as the improvement was confined to the leads reflecting infarction and the QRS duration was less than 100 ms.

In conclusion, chronic beta-blockade results in improvement of the electrocardiogram in survivors of AMI. These changes may signify improved prognosis.

Influence of cigarette smoking on morbidity, mortality, and mode of death in coronary patients

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Five hundred and eighty-nine consecutive male subjects aged less than 60 years who survived a first myocardial infarction for at least 28 days have been followed for 1 to 15 years. Treatment was based on early mobilisation and return to work, an active exercise programme, and long-term risk factor intervention.

The 5-year survival was 80 per cent and the 10-year survival was 61 per cent. Age, the severity of the initial attack, and hypertension all affected prognosis.

Smoking habits before the initial illness did not affect subsequent survival. Of the 446 initial smokers, however, those who stopped smoking had a significantly lower death rate than those who continued. This association was independent of other determinants of prognosis. Those who reduced to less than half their earlier cigarette consumption initially fared better than those who continued to smoke heavily but ultimately shared the same poor survival. The mode of death did not differ between decedents who continued to smoke and those who stopped after the initial event.

The effect of continued cigarette smoking on total (fatal and non-fatal) ischaemic events during the follow-up period was presented.

Multicentre propranolol post-infarction trial

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In a double-blind, multicentre study, 783 patients (mean age 55 years), who had sustained an anterior myocardial infarction were randomly allocated to treatment with propranolol (40 mg t.d.s.) or matching placebo. Entry time to the trial ranged from 2 to 14 days (mean 8·4 days) after infarction, with follow-up visits at 1, 3, 6, and 9 months.

The trial was designed to detect differences between the two groups at the 5 per cent significance level, with an 80 per cent chance of success. A sequential analysis was performed.

Data up to 3 months' follow-up are presented. Risk factors, independent of treatment, which reach statistical significance were age, high heart rate, and ventricular arrhythmias at trial entry, history of hypertension, and the female sex. Other risk factors were, at hospital admission, systolic blood pressure above the mean, a history of smoking, of angina, and of congestive heart failure in the pretrial entry phase.

By 1 month, 18 out of 328 patients suitable for analysis had died in the propranolol groups, compared with 14 out of 343 patients on placebo. Equivalent figures at 3 months were 22 out of 301, and 21 out of 312 respectively. There were no significant treatment effects on mode of death, reinfarction rate, or heart failure withdrawal rate.

Tricuspid atresia. Early and late problems after pulmonary artery to right atrial connection

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Between 1972 and 1977, 18 patients with tricuspid atresia aged 1 to 26 years, 12 over age 10, had various forms of right atrial to pulmonary artery connection with closure of atrial communication; six had associated transposition (TGA). Vena caval valves were used in 7. The causes of early and late mortality have been studied together with the haemodynamic findings and state of the long-term survivors. There were 8 perioperative deaths related mainly to errors in technique (5) or assessment (3). Technical problems related to reopening of atrial septum (3) with severe hypoxia, torrential haemorrhage from loosened atrial purse string suture (1), spreading thrombosis around inferior vena caval valve (1) and subaortic obstruction from restrictive ventricular septal defect in transposition of the great arteries. Assessment errors were underestimating left ventricular dysfunction (1) and not recognising and treating subaortic obstruction in 2 with normally related great arteries. Two late deaths occurred in the first year; 1 from chronic sepsis and the other was sudden and unexplained. Of the 8 survivors, 7 remain well leading normal lives and 1 has high right atrial pressure related to pulmonary artery stenoses from previous shunts. Six had the 'caval' syndrome early and in 2 it recurred with intercurrent infections. Four had reoperation: for reclosure of atrial septal defect (3) and open anastomosis (1). One has recurrent symptomatic tachycardia and 2 without caval valves have developed abnormal liver function tests. Recatheterisation in 7 showed gradients of 4 to 14 mmHg between right atrium and distal pulmonary arteries with low normal resting cardiac outputs. We conclude that this operation with careful selection and technique improves quality of life in hypoxic patients but late postoperative problems are common.

Indications and results of Fontan operation and its modifications

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Between 1975 and 1978, 6 children ranging in age from 3 to 12 years underwent a Fontan operation. Five had previous systemic-to-pulmonary artery shunts, and 1 of these had a cavopulmonary shunt.

The tricuspid valve was atretic in 4 and hypoplastic in 2 patients. An outlet chamber or hypoplastic right ventricle was found in 5 patients. The pulmonary valve was normal in 1, stenotic in 2, and atretic in 3 patients. Increasing cyanosis was the main indication for surgery. A valved atriopulmonary conduit was used in 3 cases. A valved conduit arising from the right atrium and inserted into an incision extending from the outlet chamber into the pulmonary artery was used in 2 patients. An unvalved conduit from the right atrium to the outlet chamber was constructed in 1 case. There was 1 hospital death and no late deaths. All 5 survivors followed up for 7 to 30 months have improved in symptoms and signs.

These cases indicate the feasibility of using an outlet chamber or a hypoplastic right ventricle even in the presence of pulmonary valve atresia with the intention that the power of right atrial contraction could be augmented, and they show that the indications for the Fontan operation could be extended to the surgical repair of severe forms of pulmonary atresia, intact ventricular septum, and hypoplastic right ventricle.

Complete transposition of great arteries with intact ventricular septum and left ventricular outflow tract obstruction: surgical management and anatomical considerations

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The surgical management of patients with transposition of the great arteries with intact ventricular septum (IVS) and subpulmonary stenosis remains controversial. Though direct resection of the obstruction is usually attempted, an alternative approach has been to place a conduit from the left ventricle to the pulmonary artery.

Among 130 consecutive patients undergoing Mustard's operation for repair of complete transposition at the Brompton Hospital were 5 patients in whom subpulmonary stenosis required surgical treatment. Their ages at operation ranged from 13 months to 5·3 years. Each had a combined Mustard's procedure and placement of an external conduit from the left ventricle to the pulmonary artery. There was 1 hospital death. Postoperative cardiac catheterisation performed in the survivors showed good relief of the stenosis and no significant gradient across the conduit.

Our study of the morphology of the left ventricular outflow tract in complete transposition with IVS and subpulmonary stenosis shows that the position of both the mitral valve and the conduction tissue is such that satisfactory resection of the stenosis is difficult without major risk of damaging these structures. Consequently, insertion of a conduit from the left ventricle to pulmonary artery in total correction of patients with complete transposition with IVS and subpulmonary stenosis represents a good alternative.

Fixed (discrete) subaortic stenosis—late results of resection. A congenital or acquired lesion?

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Thirty-nine patients, aged 5 to 57 years when a fixed fibrous subaortic ring was resected, were evaluated completely for 3 to 14 years.

Two late deaths occurred; one during sport and the other in congestive failure. Nineteen have maintained well-being with improved electrocardiograms. Complications were related to increasing aortic regurgitation (2) or mitral regurgitation (4), pacemaker for perioperative (3) and late block (1), worsening electrocardiogram after initial improvement (4), and reoperation for redeveloped fixed subaortic stenosis (4).

Thirty patients had postoperative catheterisation, 11 repeated. In 17, resting gradients of 5 to 45 mmHg increased to 60 to 185 mmHg with isoprenaline and the left ventricle appeared angiographically and behaved physiologically like HOCM. Thirteen showed only a slight or no increase in gradient with isoprenaline.

It is suggested that fixed subaortic obstruction might be acquired and that the important primary congenital abnormality is in the myocardium. This, when severely hypertrophied from secondary obstruction, can continue to function abnormally after complete removal of the fixed obstruction. In view of this and the secondary effects on aortic and mitral valves, fixed subaortic obstruction should be removed early as its presence may aggravate the abnormal myocardial behaviour. Survivors require careful supervision as the basic abnormality probably remains in many and causes late problems.

Critical aortic stenosis in early infancy

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Congestive heart failure caused by aortic stenosis in early infancy is invariably fatal unless surgical relief of the obstruction is achieved. Recently we have seen 6 infants aged 4 to 9 weeks with critical aortic stenosis, in all of whom the diagnosis was suspected clinically and was confirmed by echocardiography before cardiac catheterisation. One aged 8 weeks had discrete subvalve stenosis, not previously described in an infant. His M-mode echocardiogram showed characteristic, diagnostic, abnormal aortic valve leaflet motion. Five infants with valvar stenosis had diminished aortic valve cusp opening (2 to 4 mm), the echo measurement correlating accurately with angiographic and operative findings. Two-dimensional real-time echocardiography identified valve doming in the infants with valvar stenosis. Echo estimates of left ventricular pressure correlated closely with measured pressures.

All 5 infants with valvar aortic stenosis underwent successful valvotomy, 3 under hypothermia and inflow occlusion, and 2 on cardiopulmonary bypass. All are well between 6 and 15 months postoperatively. The infant with discrete subvalvar stenosis had incomplete surgical relief of the pressure gradient and died 17 days postoperatively.

Thus, echocardiography was diagnostic of aortic stenosis in 6 infants and differentiated valvar from discrete subvalvar stenosis. Aortic valvotomy provided dramatic relief of cardiac failure.

Arrhythmias and Mustard's operation

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One hundred and twenty patients with transposition of the great arteries have undergone a modified Mustard's operation to avoid damage to the sinus node and atrioventricular conducting tissue. Eighty-eight had atrial baffle alone (4 palliative) of whom 13 (14·7%) died; 32 had additional closure of ventricular septal defect and/or relief of left ventricular outflow tract obstruction with 9 deaths (28%). Of 105 discharged from hospital 101 were in sinus rhythm on standard electrocardiogram. Six had conduction disorders or arrhythmias; 2 after simple Mustard's operation were present preoperatively. The remaining 4 had complex procedures. On 24-hour electrocardiogram performed between 2 weeks and 4 years, 3 (5·8%) of 51 patients having atrial baffle alone, but 6 (35%) of 17 having complex procedures showed arrhythmias. There were 7 late deaths including 5 which were sudden and unexpected. Four of these had conduction disorders or arrhythmias on standard or 24-hour electrocardiograms. Each had complex procedures except a single patient undergoing Mustard's operation alone in whom atrioventricular block was present preoperatively.

Our data suggest that using the modified Mustard's operation postoperative arrhythmias may largely be avoided, but when additional procedures are performed arrhythmias are more frequent and may be associated with sudden death.

Exercise testing and ambulatory electrocardiographic monitoring after surgical repair of Fallot's tetralogy and ventricular septal defect

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Sudden death is a recognised complication after surgical repair of Fallot's tetralogy and ventricular septal defects, and has been associated with arrhythmias and surgically produced conduction abnormalities. To evaluate the significance of postoperative conduction disturbances and arrhythmias more fully, 50 patients who had been operated on between 1 and 11 years previously undertook maximal treadmill testing and 24-hour electrocardiograph monitoring by tape-recorder. The ages ranged from 5 to 28 years.

The standard 'Bruce' procedure was used with a short preliminary warm-up period. Taking predicted values for normal subjects for the same procedure, only 20 per cent of patients achieved average performance for same age and sex.

Six-lead electrocardiographic monitoring was carried out during and for 5 minutes after the test. Arrhythmias, other than isolated atrial and ventricular ectopic beats, were rare and included 2° AV block (1), 1° AV block (2), ventricular tachycardia (1), atrial fibrillation (1), and frequent ventricular ectopics (1). All arrhythmias were transient and required no treatment.

Twenty-four-hour electrocardiographic monitoring was carried out after the exercise test. Significant arrhythmias occurred in 2 patients, both having episodes of AV junctional tachycardia.

With these methods, arrhythmias were detected in only a small percentage of postoperative patients. Treadmill testing appears to identify arrhythmias and conduction disturbances more frequently and gives additional information on exercise performance.

Computer processed thallium-201 scintigrams during and 4 hours after maximal exercise. Significance of stenosed and occluded vessels

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Thallium-201 myocardial scintigrams were obtained during maximal exercise and data were collected continuously from the time of injection for 3 minutes. Static scintigrams were then obtained and repeated 4 hours later. Time-dependent analysis of regional distribution of thallium-201 indicated that extracardiac activity was significantly superimposed on counts obtained from the heart. Scans were, therefore, processed by a combination of subtraction and smoothing. Areas of underperfusion were defined as those with less than 50 per cent myocardial activity.

No normal scans were obtained in patients with coronary disease. All segments supplied by occluded vessels showed reduced activity during exercise; 18 per cent were normal after 4 hours and 9 per cent improved. Occlusion of the left anterior descending artery caused persistent defects. Ninety-four per cent of segments supplied by stenosed vessels showed reduced activity on exercise, but 44 per cent of these were normal after 4 hours and 17 per cent improved. Persistent defects were all associated with corresponding regional ventriculographic abnormalities. Defects with normal activity after 4 hours were always associated with a normal ventriculogram.

Computer processing significantly improved the sensitivity of thallium-201 scintigraphy and enhanced its clinical value. The method has advantages in cost and convenience when compared with conventional resting and exercise scintigraphy.

Objective non-invasive assessment of coronary artery bypass graft surgery

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Praecordial exercise mapping was used before and after coronary artery bypass graft surgery in 50 patients; 3 other patients who died within 1 month of operation were excluded.

Group 1 (35 patients) were all pain free at follow-up and none showed new praecordial Q waves. In 31 there was no praecordial ST segment depression after exercise and coronary arteriography (20 patients) showed patent functioning grafts. Four patients developed significantly smaller areas of ST segment depression postoperatively; 3 had blocked grafts and 1 had a patent though poorly functioning graft.

Group 2 (10 patients) continued to suffer from chest pain after the operation; in 8 an area of ST segment depression persisted after exercise and coronary arteriography showed that at least 1 graft in each patient was blocked. Both patients without praecordial ST depression after exercise had patent grafts.

Group 3 (5 patients) were worse after operation; 3 developed significantly greater areas of ST segment depression after exercise and the remaining 2 developed new areas of Q waves. All had at least 1 occluded graft.

While there is thus a variable relation between relief of chest pain and the development of exercise-induced myocardial ischaemia after operation, praecordial exercise mapping outlines areas of Q waves and ST segment depression that correlate well with the state of the grafts.

Value of thallium-201 exercise scintigraphy in predicting coronary artery graft status

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The value of thallium-201 exercise scintigraphy in predicting coronary artery bypass graft (CABG) status was studied in 30 patients in whom operation had been performed 2 to 5 years previously. Computer interpretation of scintiscan data allowed quantification of regional nuclide concentration. Reduction in regional count density of more than 20 per cent was considered abnormal. CABG integrity was determined by arteriography. Forty-five CABG's were placed; 24 to left anterior descending coronary artery and 21 to right coronary artery.

From scintiscan interpretation, graft patency was accepted where tracer concentration in the regions supplied by the graft appeared normal, while reduced tracer concentration in those regions implied graft occlusions.

Tracer concentrations were normal in 27 of 29 (93%) vascular areas supplied by patent grafts, while in 11 of 16 (69%) vascular areas supplied by occluded grafts, tracer concentrations were reduced. Thus, the accuracy of the scintiscan in predicting graft patency was 84 per cent and in predicting graft occlusion was 85 per cent. In addition, in 12 patients, the scintiscan identified disease in 15 native vessels where CABG had not been performed.

These results suggest that thallium-201 exercise scintigraphy can provide useful non-invasive information regarding CABG status and may serve to identify those symptomatic patients who may require further investigation.

Changes in regional myocardial lactate metabolism after coronary bypass surgery

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Obstructive coronary artery disease results in localised myocardial ischaemia and a change in metabolism from aerobic to anaerobic glycosysis with lactate production and the clinical phenomenon of angina pectoris. Estimation of the transmyocardial lactate gradient during atrial pacing stress is a sensitive method of detecting such change and regional sampling along the coronary sinus has enabled ischaemic areas to be localised.

Fifteen patients were investigated before and after saphenous vein bypass grafting by estimation of regional lactate metabolism together with selective coronary angiography. Patent grafts were associated with a distinct improvement in regional lactate metabolism, duration of atrial pacing, and subjective effort tolerance. Continuing angina with occluded grafts was associated with unchanged regional lactate metabolism. Residual abnormalities of regional lactate metabolism were observed when angina persisted despite patent grafts.

Successful coronary bypass surgery has been shown to improve regional lactate metabolism, and assessment postoperatively can localise residual ischaemic areas and guide the approach to further treatment of continuing angina.

Reoperation for recurrent angina

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Thirty-three patients with persistent or recurrent angina after coronary bypass surgery have been reoperated. Recurrent symptoms were attributed to: (a) progression of disease in ungrafted vessels or incomplete revascularisation at the first operation (6); (b) graft occlusion or stenosis (14); (c) disease distal to grafts (1); and (d) combinations of these factors (12).

Fifty-seven vein grafts were implanted and 15 vessels were endarterectomised. There was no operative mortality. Perioperative myocardial infarction occurred in 2 patients.

Patients have been followed for 3 to 61 (median 21) months. There have been no deaths. Nine are symptom free, 15 improved, but 9 unchanged.

Recurrent angina always occurred within 3 months. Of 10 patients who had grafts implanted into previously ungrafted coronary arteries, 9 are improved; of the 17 who had grafts placed to previously grafted vessels, 8 are improved, and of the 6 patients who had combined procedures, 4 benefited from the second operation.

These results indicate that a second coronary artery vein graft operation can be carried out safely, and, in selected patients, those with disease in previously ungrafted vessels, it has a good chance of a favourable result.

Risks and results of reoperation for coronary artery disease

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Since October 1971, 36 patients (34 men, 2 women) underwent reoperation for coronary artery disease (CAD); mean age at reoperation was 48 years (31 to 67). Four patients underwent a third operation. Mean time from first operation to recurrence of symptoms was 19 months (0 to 72) and from recurrence of symptoms to reoperation was 10 months (1·5 to 60). Mean number of grafts inserted at reoperation was 1·8. Operative mortality for reoperation was 9 per cent (3/36) and was unrelated to left ventricular function. No Q wave infarcts occurred at reoperation. In 33 survivors of reoperation there were 3 late infarcts, 1 fatal, and 4 underwent third operation after a mean time of 28 months (10 to 56). The remaining 28 have been followed through a mean time of 16 months (1 to 48). Thirty-three per cent (10/28) are pain free, 30 per cent (9/28) are improved, and 37 per cent (11/28) are unchanged or worse.

Review of investigations before reoperation in 26 patients showed the cause of recurrent angina to be the result of graft malfunction alone in 3/26, graft malfunction plus progression of CAD in 17/26, and progression of CAD alone in 5/26. Initial revascularisation was incomplete in 11 patients, a major vessel being unoperated in 7. In these 26 patients 6 had grafts to unoperated vessels alone, 11 had revision of grafts, and 9 patients had both.

Reoperation for coronary disease carries a higher mortality than initial operation and the results are less satisfactory, but it is justified for severe symptoms.

Serum myoglobin determination in patients with acute myocardial infarction

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The use of serum myoglobin determinations in the diagnosis and quantitation of acute myocardial infarction was studied in 49 patients. Serial blood samples, collected for the first 72 hours after pain, were analysed for serum myoglobin using a radioimmunoassay procedure. Samples were also evaluated for serum creatine kinase (CK) and its myocardial isoenzyme MB CK, aspartate aminotransferase (SGOT; AST) and α-hydroxybutyrate dehydrogenase (α-HBDH). Analysis of first and second samples obtained at $7{\cdot}6 \pm 5{\cdot}7$ and $10{\cdot}7 \pm$ (mean ± SD) hours, respectively, after pain produced the following detection rate: serum myoglobin 85 per cent and 98 per cent; serum CK 71 per cent and 85 per cent; serum AST 58 per cent and 81 per cent; serum MB CK 29 per cent and 60 per cent; serum α-HBDH 23 per cent and 33 per cent, respectively. Total MB CK and myoglobin release from damaged myocardium were calculated using the method of Norris *et al.* (1975, *Circulation* **51** (4) 614-620).

A significant correlation was obtained between infarct size calculated from MB CK and myoglobin in the whole group ($n = 29$, $r = 0{\cdot}69$, $P < 0{\cdot}001$). The correlation was even more significant for smaller infarcts with MB CK release $\leqslant 200$ U/l ($n = 13$ $r = 0{\cdot}92$, $P < 0{\cdot}001$).

In conclusion serum myoglobin determinations are more sensitive than conventional enzyme assays in the early detection of acute myocardial infarction. Total myoglobin release correlates significantly with MB CK estimates of infarct size.

Value and limitation of ergometrine in predicting vasospastic angina

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Transient vasospasm has been suggested as a cause of anginal pain in patients with angiographically normal coronary arteries. Ergometrine-induced narrowing of the coronary arteries has been advanced as a method of unmasking vasospastic angina. The response of 20 patients with normal coronary arteries to intravenous ergometrine (0·25-0·5 μg) has been assessed by quantifying the change in coronary artery dimension, regional myocardial lactate metabolism, and regional myocardial perfusion using thallium scintigraphy.

Of 10 patients with classical anginal pain, 8 had localised narrowing > 70 per cent (post-ergometrine) in 1 or more coronary arteries as well as generalised lumen reduction. All 10 had a localised abnormality on post-ergometrine thallium scintiscans and 8 out of 10 had abnormal regional myocardial lactate metabolism. In contrast in the 10 patients with atypical chest pain there was only generalised lumen reduction after ergometrine with no regional perfusion abnormality in the post-ergometrine thallium scintiscan, and lactate metabolism was normal.

In the chest pain syndrome associated with normal coronary arteries, vasospasm induced by ergometrine may be a useful predictive test for vasospastic angina if localised lumen narrowing > 70 per cent is associated with a similarly localised abnormality in regional myocardial lactate metabolism and comparable myocardial perfusion defect. Generalised lumen reduction and perfusion abnormality appears to be a normal pharmacological response to ergometrine.

Method for control of tachycardia by long-term programmed stimulation

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Two main problems have prevented therapeutic use of programmed stimulation in outpatients: (1) The stimulus generator is too large and complicated to be implanted, and an external wire from the heart is clinically unacceptable in most cases. (2) External sensing of the electrocardiogram to detect an arrhythmia is very difficult.

Our method uses a modified ventricular triggered implanted pacemaker providing a large ineffective stimulus during the refractory period in the usual way. This stimulus is easily sensed by a small external programmer which can be either automatic or held in the patient's hand.

When the programmer detects a tachycardia above a preset limit it delivers one or two appropriately timed stimuli to the skin. These are not felt by the patient but are sensed by the implanted pacemaker which at once produces one or two premature contractions to terminate the tachycardia.

Our first unit was implanted on 17 July 1978 in a patient with intractable tachycardia due to WPW syndrome, and continues to function correctly. To our knowledge this is the first report of tachycardia control by programmed stimulation on a long-term basis without the need for exteriorised electrodes. The method also enables repeated non-invasive electrophysiological studies to be performed.

Endocardial mapping and cryosurgery for arrhythmias

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Surgical treatment of arrhythmias has been extended by the introduction of cryosurgical ablation either of the accessory pathway in the Wolff-Parkinson-White (WPW) syndrome, or of the bundle of His when atrioventricular block is required. We have successfully ablated the accessory pathway in 7 cases of WPW syndrome, after epicardial mapping of the conduction patterns had indicated the location of the accessory pathways. These were left-sided (WPW type A) in 4 and right-sided (type B) in 3. Endocardial mapping, as used to locate the bundle of His, has been extended to record from both AV valve rings so as to define the accessory pathway precisely when it is subendocardial or septal. This has enabled us to identify 3 septal and 5 free-wall bypasses; one patient had 2 right-sided free-wall accessory pathways, both implicated in the arrhythmias.

Transient freezing during the arrhythmia, sufficient to cool the tissues and temporarily block the accessory pathways, made the technique more sensitive. This was then followed by permanent cryoablation. On follow-up (4 to 18 months) there was neither mortality nor significant morbidity. Arrhythmias have been completely abolished in 6 patients; in the other, the paroxysms are briefer and soon terminate spontaneously: here the accessory pathway was so near the bundle of His that temporarily cooling it also caused transient AV block.

These techniques were used in 2 further patients with atrial arrhythmias rapidly conducted via the AV node in order to define and ablate the bundle of His.

When surgery is required for refractory arrhythmias we have found combined epicardial and endocardial mapping and cryoablation to be effective.

Differentiation of ventricular ectopy from aberration

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Ventricular arrhythmias may be confused with supraventricular arrhythmias complicated by aberrant intraventricular conduction. We have compared digitised Frank vectorcardiograms in 84 patients having uniform ventricular extrasystoles with those in 32 patients with aberrant conduction produced during programmed electrical stimulation. Of these 32, 16 developed complete right bundle-branch block aberration (QRS duration $\geqslant 125$ ms) and 10 developed left bundle-branch block aberration.

The pattern of right bundle-branch aberration was only seen in ventricular extrasystoles of 4 patients; likewise ventricular extrasystoles of only 4 patients showed the pattern of left bundle-branch aberration. Ventricular extrasystoles in the remaining 76 patients could be identified as such either by an initial delay of at least 20 ms in QRS inscription or a distinctive QRS morphology on the vectorcardiogram. Furthermore, the majority of ventricular extrasystoles (51) differed from aberrant conduction either by having a predominant anterior and leftwards orientation or because they showed an initial delay of 40 ms or more. The initial slow component of the QRS complex could sometimes be identified on the conventional electrocardiogram, but was not diagnostic in single lead recordings. Vectorcardiographic studies of arrhythmias aid the electrocardiographic differentiation of ventricular arrhythmias from those of supraventricular origin that are complicated by aberration.

Sinus node disease in young people

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All known cases of sinus node disease presenting at King's College Hospital and the Royal Sussex County Hospital were reviewed. There were 9 patients under the age of 25 years (mean 19, range 15 to 24) with sinus node dysfunction in the absence of other forms of heart disease. All were male. Of the 5 with permanent pacemakers, 4 were over 1·86 m (6ft 1in) tall and 3 of the 4 patients without pacemakers were over 1·83 m (6ft 0in) in height.

Ambulatory monitoring was performed on the families of 6 of these 9 patients. Using strict criteria, conducting system abnormalities were found, or had been described previously, in at least 2 more members of 3 of the families. The abnormalities included first and second degree atrioventricular block, supraventricular tachycardias, the bradycardia/tachycardia syndrome, and sinus bradycardia requiring permanent pacing. Some members of 2 of the remaining 3 families showed possible evidence of sinus node dysfunction.

It is concluded that young people affected by sinus node disease tend to be tall men with relatives showing conducting system dysfunction. This suggests a possible hereditary factor in the aetiology of sinus node disease in young people.

Amiodarone in prophylaxis of various supraventricular arrhythmias

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Amiodarone has been advocated as the agent of choice for arrhythmias refractory to conventional drugs in those patients where there is no immediate indication for surgery. Though not commercially available in the UK amiodarone has been evaluated at various centres and we now present our experience in 21 patients with refractory supraventricular arrhythmias, all of whom had been studied electrophysiologically. Thirteen were shown to have accessory pathways, of whom 6 had overt Wolff-Parkinson-White syndrome; 4 of these 6 had recurrent atrial fibrillation with mean ventricular rates exceeding 250 a minute and the remaining 9 patients with pre-excitation had paroxysmal reciprocating atrioventricular tachycardia (PRAVT). The other 8 patients had paroxysmal atrial fibrillation or flutter conducted via the AV node. The initial dose of amiodarone (600 mg a day) was gradually reduced to the lowest level at which the patient remained symptom-free. Objective evaluation during follow-up (4 to 48 months) included frequent ambulatory electrocardiographic monitoring with or without electrophysiological testing. All patients with atrial fibrillation complicating the WPW syndrome became asymptomatic; during atrial fibrillation induced at electrophysiological testing, the mean ventricular rate did not exceed 200 a minute. In 7 of the 8 cases with atrial fibrillation unassociated with pre-excitation the arrhythmia was completely abolished. However, of those with PRAVT only 3 responded satisfactorily; 2 discontinued treatment because of early side-effects while the remaining 5 did not improve or, paradoxically, suffered more frequent episodes of tachycardia.

While amiodarone has an important and sometimes life-saving role, some patients fail to improve. Our adverse results in this group may partly reflect the type of patient referred for investigation and management.

Value of 24-hour ambulatory electrocardiographic recordings in 405 patients with dizziness, syncope, or palpitation

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Of 1000 consecutive dynamic electrocardiograms (DCG), 678 were performed for assessment of dizziness, syncope, or palpitation in 405 patients. Thirty-six of the patients had pacemakers. Sixty DCG's were technically inadequate. The recordings were classified according to the correspondence between DCG findings and symptoms noted in the patient diary. (1) Completely diagnostic: significant arrhythmias corresponding to diary symptoms (99 recordings). (2) Incompletely diagnostic: (a) absence of significant arrhythmias in the presence of diary symptoms (90 recordings); (b) presence of significant arrhythmias but no diary symptoms (197 recordings); (c) presence of significant arrhythmias corresponding to symptoms other than that for which the DCG was indicated (52 recordings). (3) Non-diagnostic: absence of both significant arrhythmias and diary symptoms (180 recordings).

Incomplete diagnostic categories were regarded as clinically valuable in that they either excluded a cardiac arrhythmia as a cause of symptoms (group 2a) or they revealed significant arrhythmias which did not correspond to diary symptoms (group 2c). The absence of symptoms corresponding to significant arrhythmias was ascribed to poor diary keeping in 54 of 197 recordings.

With careful consideration of DCG findings together with diary symptoms, DCG monitoring is very useful in detecting or excluding significant arrhythmias as a cause of dizziness, syncope, or palpitation.

Limitations of gated blood pool scintigraphy: clinical and experimental aspects

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This study was designed to investigate those factors that adversely affect radionuclide methods of evaluating ventricular function.

The value assumed for background activity is critical in the determination of ejection fraction by count rate fluctuation techniques. In 21 LAO equilibrium studies estimates of background from 2 separate periventricular regions differed by 1 to 19 (mean 9) per cent. In 12 RAO first pass studies regional differences of background were again apparent ranging from 0 to 38 (mean 16) per cent. These variations lead to significant differences in estimated ejection fraction.

Assessment of regional wall motion requires accurate edge definition. Phantom studies have disclosed that choice of isocount contour is critical if quantitative measurements of wall motion are required and that movement of such contours does not always indicate wall movement. This is further complicated by the variable background in clinical studies. Second derivative techniques are unaffected by background variation but difficulties arise because existing algorithms do not appear to be able to detect edges equally well in all directions.

Significant drawbacks still exist in the evaluation of ventricular function with radionuclides. These should be considered when using these potentially very useful techniques as a guide to decision making in individual patients.

Automated system to encourage more widespread use of quantitative ventriculography

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Extraction of information from ventriculograms usually depends on time-consuming and subjective visual impressions of ventricular size, shape, and contraction.

The use of our developed computer programmes with commercially available state-of-the-art hardware (Vickers Joyce-Loebl 'Magiscan' image analysis system) permits tackling of the whole problem of quantification by boundary recognition and subsequent computation of relevant quantities. The boundary-finding programmes involve (i) computationally intensive operations on image intensities in suspected boundary regions and (ii) extrapolations from the positions of parts of the boundary already found (in the current and in previous frames).

The system incorporates comprehensive display options for the data. The following may be shown: (i) the boundaries themselves—separately, sequentially as an animation or superimposed, (ii) measured and calculated time-varying quantities, for example volume, (iii) inward or outward movements of the segmental boundary as grey level contour maps or isometric projection.

The compact, self-contained system facilitates detailed automatic analysis of ventriculograms, will accept standard 35 mm cine film, and has been applied to similar studies with radionuclides.

Cross-sectional echocardiographic assessment of aortic valvar stenosis

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The ability of cross-sectional echocardiography directly to measure aortic valve area was assessed in patients with aortic valve stenosis. Forty-two patients (age range 6-67) were studied by short and long axis scans using a Smith Kline Echosector. Patients with significant aortic regurgitation were excluded. The appearance of the aortic root was compared with a control group of 50 patients who had normal aortic valves. Direct measurement of aortic valve area was possible in 24 patients and 11 of this group had undergone cardiac catheterisation within the preceding 3 months. Four patients within this group demonstrated on short axis scans eccentric cusp position with a single diastolic closure line characteristic of a congenitally bicuspid valve. None showed the presence of a third commissure. The mean systolic aortic valve gradient and aortic valve area (calculated at cardiac catheterisation) were compared with aortic valve area as measured directly by gross sectional echocardiography.

In the 11 patients selected there was a good correlation ($R = 0{\cdot}83$) between mean systolic gradient and aortic valve area as measured by cross-sectional echocardiography.

High resolution cross-sectional echocardiography represents a significant advance in the direct assessment of the aortic valve.

Use of fresh unstented homograft valves for replacement of aortic valve. Analysis of 8 years' experience

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Between August 1969 and May 1978, 679 patients underwent homograft replacement of the aortic valve. Isolated elective valve replacement was performed in 411 patients. Thirty-four patients had total aortic root replacement with reimplantation of the coronary arteries. There were 16 early deaths (3·9%) and 43 late deaths (10·5%) during a follow-up between 3 and 102 months (mean 47 months). Actuarial analysis showed 87 per cent survival at 5 years and 81 per cent at 8 years. Valve failure occurred in 24 patients (5·9%) due to prolapse of 1 cusp in 8 patients (2·0%), infective endocarditis in 7 patients (1·7%), and degeneration of the valve in 9 patients (2·2%). Degenerative valve failure was encountered after the fourth year with an incidence of 4·8 per cent of patients at risk and occurred only in grafts from donors over the age of 70 years. Diastolic murmurs were present in 28 per cent of patients followed beyond 1 month and increased very slightly with time. Systemic embolism was not recorded in any patient in spite of the fact that anticoagulants were not used. The clinical result was judged to be good or excellent in 90 per cent of patients. It is concluded that homograft replacement of the aortic valve gives satisfactory results with a low incidence of late valve failure.

Correlation of echocardiographic, surgical, and pathological findings in mitral regurgitation

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The ability of echocardiography (echo) to determine the aetiology of mitral regurgitation was assessed in 62 patients by comparing echocardiographic, surgical, and pathological findings.

A floppy mitral valve was found at surgery in 22 patients, 17 showing echocardiographic evidence of mitral valve prolapse. There was only a mild or moderate degree of abnormality of the mitral cusps in 3 patients without echo evidence of prolapse. In the remaining 2 patients the echo findings were technically inadequate.

Chordal rupture was detected by echo in all 8 patients with rupture of chordae to the central scallop of the anterior cusp but in only 4 of 8 cases involving the central scallop of the posterior cusp. Echocardiographic abnormalities were seen in 3 out of 4 patients with ruptured chordae to the medial or lateral scallops.

Rheumatic mitral regurgitation was diagnosed correctly in 30 out of 31 patients. The mitral valve echo was normal in all 4 patients with mitral regurgitation to left ventricular dysfunction. The echo failed to detect perforation of the anterior mitral cusp secondary to aortic endocarditis or congenital cleft of the anterior mitral cusp.

Thus echocardiography correctly determined the pathogenesis of mitral regurgitation in 54/62 patients and this may be helpful in planning the treatment of these patients.

Fibrinolytic activity on Monday and on other days of the week

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A consistent finding of several studies is that ischaemic heart disease mortality and incidence are slightly but significantly higher on Mondays than on other days. In a week-long study of 81 men aged 40 to 49 working at a factory on the outskirts of Glasgow, and seen in a random order, whole blood fibrinolytic activity (expressed as 100/lysis time in hours) in the 17 seen on Monday was 10·0, compared with 19·7 in the 64 seen on Tuesday-Friday ($P < 0{\cdot}001$). Corresponding figures for plasma fibrinogen were 3·16 g/l and 2·78 g/l, though this difference is not significant at a conventional level. There were no differences in a wide range of other haemostatic variables, or in blood cholesterol or triglyceride levels, but the mean γ-glutamyl transpeptidase level in those seen on Monday was 32·4 IU/l compared with 23·3 IU/l in the others ($P < 0{\cdot}05$). In contrast to the Glasgow findings, no differences by day of the week were found in London men in the Northwick Park Heart Study. Increased food, tobacco, and alcohol consumption at the weekend could account for some of the Monday excess in the occurrence of ischaemic heart disease; in some situations, this excess may be partly mediated through temporarily impaired fibrinolytic activity and perhaps also through increased levels of plasma fibrinogen.

Exercise electrocardiographic and 48-hour ambulatory electrocardiographic monitor assessment of arrhythmia on and off beta-blocker therapy in hypertrophic cardiomyopathy

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Submaximal treadmill exercise electrocardiography and 48-hour continuous ambulatory electrocardiographic monitoring of 17 patients both on and off beta-blocker therapy was performed.

During 48-hour ambulatory electrocardiographic monitoring on treatment 12 patients had frequent ($\geqslant$10/1000 QRS) ventricular extrasystoles (VES), 5 of the 12 were multiform, and 3 patients had occasional ($<$10/1000 QRS) ventricular extrasystoles; 7 patients had frequent atrial extrasystoles and 4 patients had occasional atrial extrasystoles; 4 patients had occasional supraventricular tachycardia, 1 had frequent supraventricular tachycardia, and 1 had ventricular tachycardia (VT > 3 VES in a row).

During 48-hour ambulatory echocardiographic monitoring off treatment: 11 patients had frequent ventricular extrasystoles, 5/12 were multiform, and 4 had occasional ventricular extrasystoles; 5 patients had frequent atrial extrasystoles and 6 patients occasional atrial extrasystoles; 3 patients had occasional supraventricular tachycardia, 1 patient had frequent supraventricular tachycardia, and 1 patient had ventricular tachycardia.

During treadmill exercise electrocardiography on treatment 9 patients had occasional ventricular extrasystoles and off treatment 11 patients had occasional ventricular extrasystoles and 1 patient frequent ventricular extrasystoles. On exercise testing no patient had atrial extrasystoles, supraventricular tachycardia, or ventricular tachycardia.

Ambulatory electrocardiographic monitoring showed that 11 of 17 patients with hypertrophic cardiomyopathy had frequent serious arrhythmias which were not detected during exercise electrocardiograph testing. As occult arrhythmia may be the cause of sudden death in hypertrophic cardiomyopathy it is important to detect these patients, because specific antiarrhythmia treatment may improve prognosis. In this study, however, beta-blocker therapy had no significant effect on the frequency of the arrhythmias.

Assessment of myocardial ischaemia in ambulatory patients with daily chest pain

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Twenty-four hour recordings of the electrocardiogram have been used to study 100 ambulatory patients with daily angina. These patients underwent 16 point electrocardiographic mapping during exercise and all showed praecordial areas of pathological ST segment depression. Forty-five per cent of the patients showed maximum ST depression at the conventional position V5 but 35 per cent showed no changes at this position. In the remaining 20 per cent V5 was on the edge of the praecordial area and showed less severe ST depression than the central position.

The Oxford electrocardiograph recorder and high speed analyser were used for 24-hour recording of ST segment changes. The technical requirements were examined in detail. The exploring electrode was placed on the praecordial position showing the earliest and maximum changes in the ST segment during the exercise test. A mean of 14 ± 3·0 episodes of ST depression was detected in each patient. Only 16 ± 4·0 per cent of these episodes were accompanied by reported chest pain. More episodes occurred between 4 and 6 am than during any other 2-hour period during the night ($P < 0·01$). In those patients in whom V5 was on the edge of the exercise-induced area of ischaemia exploring electrodes were placed on V5 and the central position showing maximum ST changes. These simultaneous 24-hour recordings showed that V5 detected only 14 ± 4·0 per cent of the episodes of ST depression recorded at the central position.

This method provides objective information about the frequency, timing, and severity of myocardial ischaemia during the daily activities of patients with ischaemic heart disease. More information is obtained in each patient when the exploring electrode is placed on the praecordial position showing the earliest and maximum ST segment depression during exercise.

Ischaemic-like electrocardiogram in asymptomatic men with normal coronary arteriogram: studies by atrial pacing, adrenaline infusion, and autonomic blockade

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We have previously described a bimodal T wave response to intravenous adrenaline infusion (0·027-0·18 μg/min per kg) in 20 asymptomatic men whose resting electrocardiogram showed changes indistinguishable from those of myocardial ischaemia but with normal coronary arteriogram. It was suggested on the basis of *in vitro* experiments that these T changes may result from action potential changes of opposing direction in different parts of the heart. The facility by which these changes were manipulated by low doses of adrenaline and the beta-blocking agent oxprenolol (Trasicor) together with plasma sampling suggested an altered response to catecholamines rather than hypersecretion.

Adrenaline probably influences action potential duration by modifying pump activity which *in vitro* studies suggest is rate dependent. Therefore the relation between such T changes, heart rate, and autonomic activity was studied in a further 30 similar subjects by atrial pacing and low dose adrenaline infusion (0·027-0·049 μg/min per kg) alone and in combination with and without beta-blockade (propranolol 0·2 mg/kg) and atropine (0·04 mg/kg). ST-T changes, as a result of increasing heart rate by atrial pacing during constant infusion of adrenaline, were far in excess of the sum of changes resulting from heart rate increase alone and infusion alone. The combination frequently reproduced the false positive exercise test which was observed in 30 per cent, though in none after oxprenolol. Beta-blockade abolished the effects of adrenaline but not those of rate change.

Pattern of disturbed regional myocardial perfusion in patients with coronary artery disease

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Twenty patients with angina pectoris were studied using coronary arteriography and imaging of changes in regional myocardial perfusion using $^{81}Kr^{m}$. This was done to test the physiological interpretations made using the arteriogram and to describe the changes in regional perfusion in relation to stress, the electrocardiogram, and chest pain. Continuous quantification of regional count rates was used to record changes in areas of the heart thought to be supplied by normal, minimally diseased ($\leqslant 50\%$), and severely diseased ($\geqslant 70\%$) arteries. A standardised atrial pacing test was used. Four patients thought to have normal coronary arteries showed uniform distribution of perfusion. A further 6 were thought to have minimally diseased vessels but 4 of these showed significant regional inequalities of myocardial perfusion on pacing ($P = <0 \cdot 01$). Ten patients with $\geqslant 70$ per cent stenosis of 1, 2, or 3 vessels all had inequalities of regional perfusion with pacing. However, the radiologist and cardiologist were unable to predict which region would be affected except in 3 patients with single vessel disease. Regional perfusion was disturbed at the onset of pacing in all the patients with coronary artery disease. Pathological ST segment depression was noted at 140 ± 30 seconds and pain was noted at 4 minutes ± 45 seconds.

In conclusion, the coronary arteriograms did not provide an accurate physiological assessment of stenosed coronary arteries. Small increases in heart rate (that is oxygen requirements) were always accompanied by an immediate redistribution of myocardial perfusion. Therefore, an early fall in regional perfusion does not necessarily mean that the ischaemic episode is caused by coronary spasm.

Glyceryl trinitrate vs post-ectopic potentiation in assessment of ischaemic left ventricle

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Eight patients underwent a study designed to assess the relative effects of post-ectopic potentiation (PE) and glyceryl trinitrate on the ischaemic left ventricle.

The study consisted of two left ventricular angiograms each performed at the same atrial paced rate (100 bpm) and interrupted by a controlled paced right ventricular ectopic. The first angiogram was performed after pacing-induced angina and the second after glyceryl trinitrate.

Each patient thus provided an ischaemic sinus beat, an ischaemic post-ectopic potentiation beat, a glyceryl trinitrate beat, and a glyceryl trinitrate post-ectopic potentiation beat for analysis.

For the ischaemic sinus beat average ejection fraction was 0·33 (0·08) ischaemic post-ectopic potentiation beat 0·49 (0·07), glyeryl trinitrate beat 0·57 (0·08) and glyceryl trinitrate post-ectopic potentiation beat 0·71 (0·02), the differences being highly significant in all 4 groups. Segmental wall motion analysis showed that post-ectopic potentiation increased inward systolic movement in the ventricle overall whereas the increase in ejection fraction due to glyceryl trinitrate was as a result of regional as distinct from overall improvement. Two patients who did not develop angina showed no significant change in wall motion after glyceryl trinitrate whereas post-ectopic potentiation increased overall inward movement.

It is concluded that: (1) glyceryl trinitrate is more effective than post-ectopic potentiation in increasing inward systolic movement in the acutely ischaemic left ventricle; (2) post-ectopic potentiation increases inward systolic movement in all areas whereas the effect of glyceryl trinitrate is seen regionally; (3) in the 2 patients who did not develop angina the post-ectopic ejection fraction was higher than the glyceryl trinitrate ejection fraction.

Relation of isovolumic relaxation to left ventricular wall movement in man

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The duration of isovolumic relaxation and its relation to left ventricular wall movement was determined in 14 normal subjects, 44 patients with coronary artery disease, 16 with hypertension, and 10 with mitral stenosis, by performing and digitising simultaneous echo-, phono-, and apex cardiograms. In normals, aortic valve closure (A2) occurred 40 ± 10 ms before minimum left ventricular dimension, and the duration of isovolumic relaxation, from A2 to mitral cusp separation, was 65 ± 15 ms. In hypertension the timing of A2 was normal, but isovolumic relaxation prolonged to 105 ± 25 ms, causing significant delay in mitral valve opening. In coronary artery disease, A2 was delayed by 5 ± 40 ms after minimum dimension with corresponding delay in mitral opening (80 ± 35 ms), since the duration of isovolumic relaxation was normal. Delayed A2 was closely correlated with abnormal wall movement during isovolumic contraction, because of incoordinate left ventricular function. In mitral stenosis, A2 was delayed (30 ± 35 ms), but isovolumic relaxation was short allowing reduced rate of dimension increase due to left ventricular hypertrophy to be distinguished from that due to mechanical obstruction to inflow. Though mitral valve opening is delayed in both hypertension and coronary artery disease, in the former it is because of abnormal relaxation, and in the latter primarily because of prolonged ejection caused by incoordinate systolic function.

Biplane first pass radionuclide ventriculography in assessment of wall motion abnormalities in patients with acute myocardial infarction

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Thirty-five patients were studied by first pass radionuclide angiography in both right and left anterior oblique projections (RAO and LAO), between 5 and 8 days after acute myocardial infarction. Left ventricular ejection fraction (LVEF) was measured in both obliques from the time activity curve over the left ventricular region of interest, and the values correlated closely ($r = 0{\cdot}85$). There was good correlation between mean LVEF thus obtained, and LVEF calculated from the ventricular perimeters using a biplane area—length formula ($r = 0{\cdot}89$).

The extent of akinesis, expressed as the mean percentage of the end-diastolic circumference from both obliques showed a significant negative correlation with mean LVEF ($r = 0{\cdot}81$), as did that from a single RAO projection ($r = 0{\cdot}81$). A single plane LAO projection produced a less good correlation ($r = 0{\cdot}58$).

The LAO showed akinetic areas not identified in the RAO in 1 of 10 patients with anterior infarction, and in 2 of 9 with inferior infarction. Of 16 patients with combined areas of infarction, the LAO showed areas of akinesis not seen in the RAO, in 9. However, only 3 patients exhibited defects in the LAO following a normal RAO study.

Biplane radionuclide angiography improves the non-invasive detection of akinesis especially when multiple areas of infarction are present and may provide another approach to the scintigraphic assessment of infarct size.

Ventricular function in response to cold pressor test: assessment using multiple gated acquisition on technetium-99m labelled cardiac blood pool (MUGA-99Tcm) in normal subjects and patients with ischaemic heart disease

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A preliminary study was performed in 10 normotensive patients admitted for coronary arteriography (5 normals, 1 patient with cardiomyopathy, 4 patients with ischaemic heart disease) to assess the effect of the cold pressor test on ventricular wall motion and ejection fraction measured by MUGA-$99Tc^m$.

Nine subjects had normal left ventricular function at rest. A significant increase in mean heart rate and blood pressure occurred in all subjects after immersion of their hands in ice-cold water. No patient had angina during the intervention. MUGA-$99Tc^m$ was performed before and during the cold pressor test and the studies compared: (a) Normal subjects had no change or an increase in left ventricular ejection fraction and preserved normal myocardial wall motion; (b) The patient with early congestive cardiomyopathy had a reduction in left ventricular ejection fraction; (c) All patients with ischaemic heart disease had a decrease in left ventricular ejection fraction and 2 patients developed localised ventricular akinesis in a region supplied by a severely stenosed coronary artery.

It is concluded that the cold pressor test provides a stimulus sufficient to unmask latent myocardial ischaemia and produces ventricular contraction abnormalities detectable by MUGA-$99Tc^m$. This non-invasive intervention may be a new tool in the early detection of coronary disease.

Left ventricular function in postpartum cardiac failure syndrome of northern Nigeria

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Forty-three patients presenting with postpartum cardiac failure were studied. All patients had an echocardiogram on admission, and 10 patients had had right heart catheterisation. Despite gross peripheral oedema, left ventricular function, assessed by echocardiography (mean VCF = 1·2 ± 0·4; ejection fraction 50 ± 13%) and systolic time intervals (PEP/LVET = 0·41 ± 0·08), was relatively good. The estimated stroke volumes (100 ± 46 ml) and cardiac outputs (11·4 ± 4·4 l/min) were high. At catheterisation the pressures were high and the cardiac output, measured by the thermodilution technique, in 6 patients was 6·3 ± 1·5 l/min. No patient had a low cardiac output.

These findings are not compatible with a severe heart muscle disorder or cardiomyopathy. It is suggested, therefore, that in the majority of patients the primary event is fluid retention (caused by the postpartum practices of taking high sodium diets and lying on heated beds), leading to circulatory congestion which produces the gross oedema and signs of 'heart failure'.

Sarcoid heart disease in United Kingdom

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The study of sarcoid heart disease reported in 1974 has continued. At the end of June 1978, 128 patients were included; 50 of these were from East Anglia and it is suggested that cases from elsewhere are not being fully reported.

The common presentations in these patients were heart block, ventricular arrhythmia, myocardial failure, sudden death, and simulating myocardial infarction. Details of these patients were presented. Though sarcoidosis was present in other organs, it was often inconspicuous—even at necropsy.

Forty-five necropsies were carried out in the 57 patients who have died. Twenty-three of these were not diagnosed in life and 36 died suddenly.

The 71 survivors vary from those with transient rhythm disturbances to others with permanent complete heart block or congestive cardiac failure. Twelve are being paced. Treatment of this condition was discussed.

The diagnosis of sarcoid heart disease will only be made if there is a high index of suspicion and histological confirmation is diligently sought in any unusual form of heart disease, particularly with rhythm problems.

Diagnosis of obstructive and non-obstructive hypertrophic cardiomyopathy: is echocardiography of value?

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The purpose of the study was to elucidate the echo features in hypertrophic cardiomyopathy (HCM), and to assess their reliability as diagnostic criteria and as predictors of obstructive versus non-obstructive form. M-scan echocardiography was performed on 70 patients with angiographically proven HCM. The number of abnormal indices: intraventricular septal (IVS) thickness and amplitudes; IVS/LV posterior wall ratio (IVS/LVPW); LV end-systolic dimension; anterior displacement of mitral valve (IVS-C); systolic anterior motion of mitral valve (SAM); mid-systolic closure of the aortic valve (MSCAV) was scored for each patient. Each of these 7 indices was abnormal in 50 to 80 per cent of patients except IVS-C, which was abnormal in 30 per cent. Sixty-five per cent of patients with obstruction had five or more abnormal indices. Comparing the obstructive and non-obstructive groups, the proportion of patients with 5 or more abnormalities was different ($P < 0·001$). In these 2 groups the proportion of patients with SAM, MSCAV, and IVS-C was different ($P < 0·005$ for each index); however, the proportion of patients with an abnormal IVS/LVPW was not different.

The results suggest no single M-scan echo index is consistently abnormal in either obstructive or non-obstructive HCM. The presence of SAM or MSCAV in HCM appears to predict the obstructive form of disease versus the non-obstructive, whereas an abnormal IVS/LVPW ratio does not.

Assessment of chest pain in hypertrophic cardiomyopathy by thallium-201 myocardial scintigraphy

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Exercise thallium-201 myocardial scintigraphy was performed in 23 patients with hypertrophic cardiomyopathy, 18 of whom had chest pain. In selected patients further myocardial scintigrams were acquired after several hours. Coronary arteriograms were performed in 16 patients and were normal.

Abnormal scintigrams were found in 18 patients. Three had an abnormal distribution of tracer entirely attributable to septal hypertrophy (group A), whereas 15 had discrete uptake defects difficult to explain on the basis of muscle hypertrophy alone (group B). In group B 3 scintigraphic patterns were identified: (1) In 10 patients 14 defects were seen in the exercise scintigrams but not in the delayed images. Eight of these patients had chest pain. (2) In 3 patients tracer defects were seen only in delayed images and were not apparent in the initial scintigrams. One patient had chest pain. (3) Finally, 4 patients had uptake defects seen in both initial and delayed images. One patient had chest pain.

Chest pain occurred in 8/10 patients with scintigraphic evidence of ischaemia but was present in only 3/13 patients with non-ischaemic scintigrams ($P = 0{\cdot}01$).

These findings suggest that regional myocardial ischaemia occurs in hypertrophic cardiomyopathy during exercise and may account for the chest pain in this condition.

Haemodynamic effects of angiotensin blockade after cardiopulmonary bypass

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A possible relation between raised levels of angiotensin II (AII) and the vasoconstriction associated with cardiopulmonary bypass has recently been suggested. Previous studies have shown that AII levels rise conspicuously during bypass and that a significant correlation exists between the rise in AII levels and the rise in peripheral vascular resistance index (PVRI). The haemodynamic effects of SQ 14225, a specific blocker of the enzyme which converts angiotensin I to angiotensin II, have been studied.

Adult mongrel dogs (20 to 25 kg) were submitted to 60 minutes of non-pulsatile bypass at a mean perfusion pressure of 70 mmHg. Two hours after bypass, a 20-minute infusion of SQ 14225 at 2 μg/hr/per kg was given. Arterial blood pressure, left atrial pressure, cardiac index (by dye dilution), and PVRI were measured before and after 10 minutes and 20 minutes. Plasma AII was measured at control and at 20 minutes.

Mean arterial pressure fell during infusion from 103 mmHg to 82 mmHg ($P < 0{\cdot}05$). PVRI fell from 38·27 units to 21·70 units ($P < 0{\cdot}05$) and cardiac index rose from 3·00 l/min per m^2 to 3·98 l/min per m^2 ($P < 0{\cdot}05$). Mean plasma AII fell from 56·75 to 11·5 pg/ml (normal values 35 pg/ml).

These results confirm that angiotensin II is a major causative factor in the vasoconstriction associated with cardiopulmonary bypass, and indicate that reduction of raised AII levels in the postoperative period results in a significant fall in peripheral vascular resistance and a significant rise in cardiac index.

Salbutamol in treatment of heart failure

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The use of the beta$_2$-agonist salbutamol has been assessed in the treatment of patients with chronic heart failure. Nine patients, 7 men, 2 women; age range 31 to 67 years, were studied for up to 7 hours after the oral administration of 8 mg salbutamol. Cardiac output was measured by thermodilution. Pulmonary artery end-diastolic pressure (PAEDP) was recorded with a catheter and blood pressure with a sphygmomanometer. The mean cardiac output was 3·4 l/min (cardiac index = 1·9 l/min per m^2) under control conditions and rose in all patients. The mean increment was 1·5 l/min ($P < 0{\cdot}001$). The mean PAEDP fell from 19·5 mmHg to 17·0 mmHg (NS). The mean systemic vascular resistance decreased from 26·4 units to 16·5 units ($P < 0{\cdot}001$). Heart rate increased by an average of 6 beats/min (NS). These effects were similar to those in patients given intravenous salbutamol. The effects of oral salbutamol (4 mg qds) after 4 weeks were assessed. In 5 patients there was no significant change in resting cardiac output, PAEDP, exercise tolerance, or echocardiographic left ventricular dimensions.

Oral salbutamol may be of benefit in the treatment of patients with chronic heart failure. The haemodynamic effects are primarily attributable to vasodilatation.

Haemodynamic effects of sublingual isosorbide dinitrate and oral salbutamol alone and in combination in patients with severe chronic congestive cardiac failure

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Isosorbide dinitrate (ISDN) is effective in the treatment of patients with congestive cardiac failure (CCF). To determine possible augmentation of the effects of ISDN by salbutamol, haemodynamic measurements were made in 5 patients with severe chronic CCF who received ISDN 5 to 10 mg sublingually and salbutamol 4 mg orally alone and in combination.

ISDN reduced mean left ventricular filling pressure (LVFP) from 26 mmHg to 17 mmHg (23%, $P < 0{\cdot}02$) and increased mean cardiac index (CI) from 1·7 to 2·1 l/min per m^2 (23%, $P < 0{\cdot}05$), with no significant change in mean heart rate (HR) or systemic arterial pressure (AP).

Salbutamol increased CI from 1·8 to 2·2 l/min per m^2 (22%, $P < 0{\cdot}01$) 30 to 40 minutes after administration. There was no significant change in LVFP, HR, or AP.

Compared with control, combined ISDN and salbutamol reduced LVFP from 25 mmHg to 18 mmHg (28%, $P < 0{\cdot}001$) and increased CI from 1·8 to 2·5 l/min per m^2 (39%, $P < 0{\cdot}01$) with no significant change in HR or AP.

The reduction in LVFP by combined therapy was similar to ISDN alone but the increase in CI was significantly greater than either ISDN alone (19%, $P < 0{\cdot}001$) or salbutamol alone (14%, $P < 0{\cdot}05$).

Combined sublingual ISDN and oral salbutamol act synergistically to improve left ventricular performance in patients with severe chronic CCF.

Haemodynamic effects of hydralazine at rest and during exercise in patients with impaired left ventricular function

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The administration of vasodilator drugs has been shown to have beneficial effects at rest in patients with acute and chronic heart failure. To determine the efficacy of hydralazine during exercise, 6 severely symptomatic patients with chronic left ventricular failure from diffuse coronary disease or cardiomyopathy were studied at rest and during upright exercise on a bicycle ergometer. All patients were already receiving optimal treatment with digitalis and diuretics. At rest, mean arterial pressure fell from 89 ± 1·5 (SEM) to 65 ± 9 mmHg 2 to 3 hours after 75 mg hydralazine ($P < 0{\cdot}01$) and wedge mean fell from 16 ± 4·7 to 10 ± 5 mmHg ($P < 0{\cdot}01$). Systemic vascular resistance fell from 25 ± 2·1 to 11 ± 0·8 units ($P < 0{\cdot}01$). Stroke volume index increased from 24 ± 2·5 to 38 ± 4·1 ml/m^2 ($P < 0{\cdot}01$). During maximal exercise, mean arterial pressure fell from 91 ± 11 to 78 ± 6 mmHg 2 to 3 hours after 75 mg hydralazine ($P < 0{\cdot}01$) and wedge mean fell from 32 ± 4·1 to 22 ± 4·2 ($P < 0{\cdot}01$). Systemic vascular resistance fell from 13 ± 1·2 to 9 ± 0·6 units ($P < 0{\cdot}01$). Stroke volume index increased from 31 ± 3·6 to 43 ± 4·9 ml/m^2 ($P < 0{\cdot}01$).

These findings show that hydralazine administration not only results in a beneficial effect on cardiac function at rest but that this effect is sustained during upright exercise in patients with impaired left ventricular function, thus providing strong support for its use in the long-term management of such patients.

Echocardiographic features of anomalous systemic and coronary venous return

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Identification of abnormalities of the coronary sinus and the investigation of anomalous systemic venous return is described using echocardiography.

Five patients with angiographic documentation of anomalous systemic venous return including coronary sinus abnormalities are presented. A further patient with congenital absence of the coronary sinus and suspected anomalies of systemic venous drainage was also studied.

M-mode cross-sectional and contrast echocardiograms (by injecting normal saline or indocyanine green into peripheral veins) were recorded using a Smith Kline Echosector. In 3 patients with persistent left superior vena cavae (LSVC) an enlarged coronary sinus was identified by injection of contrast from a left arm vein, injection from the right arm failing to opacify the coronary sinus. In 2 further patients with complex congenital heart disease and a persistent LSVC, entry of contrast into the left-sided atrial chamber was observed after the left arm injection but not from a right arm vein injection. In the patient with congenital absence of the coronary sinus and suspected anomalous venous return contrast cross-sectional echocardiography suggested normal venous return which was later confirmed angiographically.

This study shows the potential value of cross-sectional echocardiography combined with peripheral vein contrast injections in the assessment of patients with suspected anomalies of systemic and coronary venous return.

Identification of atrial septal defects by cross-sectional contrast echocardiography

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The interatrial septum (IAS) may be visualised using cross-sectional echocardiography, and the reliability of this technique in detecting defects in the IAS was assessed.

Ten patients with ostium secundum or sinus venosus atrial septal defects (ASD) were studied using a Smith Kline Echosector and the images of the IAS compared with those obtained in a control group of 10 normal patients. In all patients contrast echocardiography was performed using normal saline or indocyanine green injected into a peripheral vein, the passage of echos through the heart being recorded.

Apparent defects of the IAS were observed in all patients with ASDs and in six of the ten control subjects. A characteristic appearance of the edge of the septal defects distinguished the two groups. With bolus injections, contrast echoes were seen crossing the IAS from right to left in all patients with IAS defects. In 4 patients who were clinically cyanosed, free transfer of echoes was observed into the left atrium and rapidly appeared within the aortic root. In patients with intact IAS no contrast was observed within the left atrium. Though cross-sectional echocardiography may suggest the presence of defects in the IAS, the use of contrast echocardiography provides confirmation of an ASD and a potential evaluation of the direction of shunting.

Study of cardiac rhythm in healthy newborn infant

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Twenty-four-hour electrocardiographic recordings were performed on 134 randomly selected infants who weighed over 2·5 kg at birth. The mean highest heart rate, measured over 9 beats, was 175 ± 19 b.p.m. The mean lowest heart rates when measured over 3, 5, and 9 beats were 82 ± 12, 87 ± 12, and 93 ± 12, respectively. At their lowest rates 109 infants had sinus bradycardias. Nineteen had atrial and 6 had junctional escape rhythms. Changes in P wave configuration occurred in 33 infants. All 24-hour electrocardiograms showed sudden slowing of rate with sinus pauses or patterns resembling sinuatrial Wenkebach block. Though 19 infants had extrasystoles only one had more than 12 per hour. Three infants had bradycardias of more than 2 standard deviations below the mean lowest rate. The first had a bradycardia of 42 b.p.m. associated with extrasystoles and including an asystolic pause of 1·8 s. The second whose only previous sib had died of the 'sudden infant death syndrome' had a bradycardia of 59 b.p.m. The third infant, who had shown cyanotic episodes during the recording, had simultaneous bradycardias of 61 b.p.m.

By providing adequate normal data this study allows the accurate interpretation of heart rhythm changes in both healthy and sick neonates.

Non-invasive diagnosis of infundibular right ventricular outflow tract obstruction

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Clinical recognition of infundibular pulmonary stenosis, often associated with other cardiac abnormality, may be difficult. In this study echo and phonocardiographic findings were analysed in 18 patients. The aetiology of the infundibular obstruction was congenital (13), hypertrophic cardiomyopathy (3), and glycogen storage disease or tumour infiltration (2). The pulmonary valve was visualised in 17 patients and with the exception of 1 patient with coexisting pulmonary valve stenosis showed abnormal motion with early or mid-systolic partial closure and fluttering of the posterior cusp. Normal valve motion was found in 4 patients after successful infundibular resection, and persistent echocardiographic abnormalities were seen in 1 patient with residual obstruction.

Late pulmonary valve closure (P2) was shown in 14 patients by phonocardiography (12) or echocardiography (2), and the magnitude of the infundibular gradient correlated with the degree of delay of P2. An increase in intensity of the systolic murmur during expiration was recorded in all 3 patients with hypertrophic cardiomyopathy. An ejection sound was uniformly absent except in the patient with coexisting pulmonary valve stenosis.

The results show that the presence of infundibular stenosis can be predicted echocardiographically and its severity assessed from the degree of delay of pulmonary valve closure.

Epidemiological study of blood pressure in infancy

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Systolic blood pressure has been measured using the Doppler ultrasound technique in a population of 2000 infants at ages 4 days, 6 weeks, 6 months, and 1 year. Systolic blood pressure (infants awake) increased from 75 mmHg at 4 days to 95 mmHg at age 6 weeks and then did not alter till age 1 year. Systolic blood pressure was 7 mmHg higher in infants awake than those asleep. It was positively correlated with weight and was not related to sodium intake.

Repeated measurements showed that systolic blood pressure was significantly correlated ($r = 0{\cdot}3$) between the ages of 6 months and 1 year even after allowing for the effect of weight. At age 6 months (though not before) it was possible to show a familial correlation between the blood pressures of the child and the child's mother, and at age 1 year between the blood pressures of the child and the child's father. Our evidence indicates that children show a tendency to develop a systolic blood pressure related to their expected blood pressure in adult life by the age of 6 months.

Effects of long-term beta-adrenoreceptor blockade in rabbits

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The effect of prolonged administration of the beta-adrenoreceptor blocking drugs timolol and propranolol on growing rabbits (starting weight 2·0 to 3·0 kg) has been studied. Drugs were administered in equivalent doses for 8 weeks. Rabbits given dl propranolol (2 mg/kg bd) intraperitoneally showed a reduced growth rate, whereas rabbits given the same drug subcutaneously, or timolol (0·2 mg/kg bd) intraperitoneally grew at the same rate as controls. Animals with a reduced growth rate ate less than animals growing normally.

Subsequently, growing rabbits were given either d- or l-propranolol (1 mg/kg bd) intraperitoneally. No reduction in growth rate was seen compared with controls.

The water content of both skeletal and ventricular muscle and heart weight to body weight ratio showed no difference between treated and untreated animals, suggesting no evidence of gross morphological change associated with chronic beta-adrenoreceptor blockade.

We believe the effect of propranolol on growth and food intake is unrelated to its beta-blocking or membrane stabilising properties. The intraperitoneal route of injection alone does not account for the effects, which may be related to levels of a specific metabolite of propranolol present when given at the higher dose.

Cardiovascular and sympathetic adaptation with bicycle exercise

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We have investigated how plasma noradrenaline, blood pressure, and heart rate change during and after bicycle exercise (mean workload 110 watts) in 11 patients (mean age 41 years; 5 normotensives, 6 mild hypertensives). Arterial pressure was recorded directly from the brachial artery and forearm venous plasma noradrenaline measured by a sensitive radioenzymatic method (Henry *et al.*, 1975). During upright exercise, mean maximum heart rate was 144 ± 7 bpm (mean ± SEM) and plasma noradrenaline approximately doubled. On stopping exercise, blood pressure and heart rate decreased rapidly while plasma noradrenaline increased in all subjects, the mean increase from 8·92 ± 1·71 to 11·87 ± 2·24 nmol/l being statistically significant ($P < 0{\cdot}005$). In comparison, in 5 of 6 patients who performed supine bicycle exercise, plasma levels fell by 2 minutes after exercise, the mean levels decreasing from 4·43 ± 4·78 to 3·01 ± 1·06 nmol/l.

We suggest that the mechanisms causing an increase in plasma noradrenaline during and after exercise are different and that the increase after upright exercise reflects increased sympathetic activity mediated by sino-aortic baroreflexes. These observations may explain why arrhythmias occur more commonly after stopping exercise. Increased alpha-adrenergic influences on bronchial smooth muscle after exercise may explain the time of onset of exercise-induced asthma.

Reference

Henry, D. P., Starman, B. J., Johnson, D. G., Williams, R. H. (1975). A sensitive radioenzymatic assay for norepinephrine in plasma and tissues. *Life Sciences*, **16**, 375.

Nocturnal blood pressure in hypertensives and effects of alpha- and beta-adrenergic blockade

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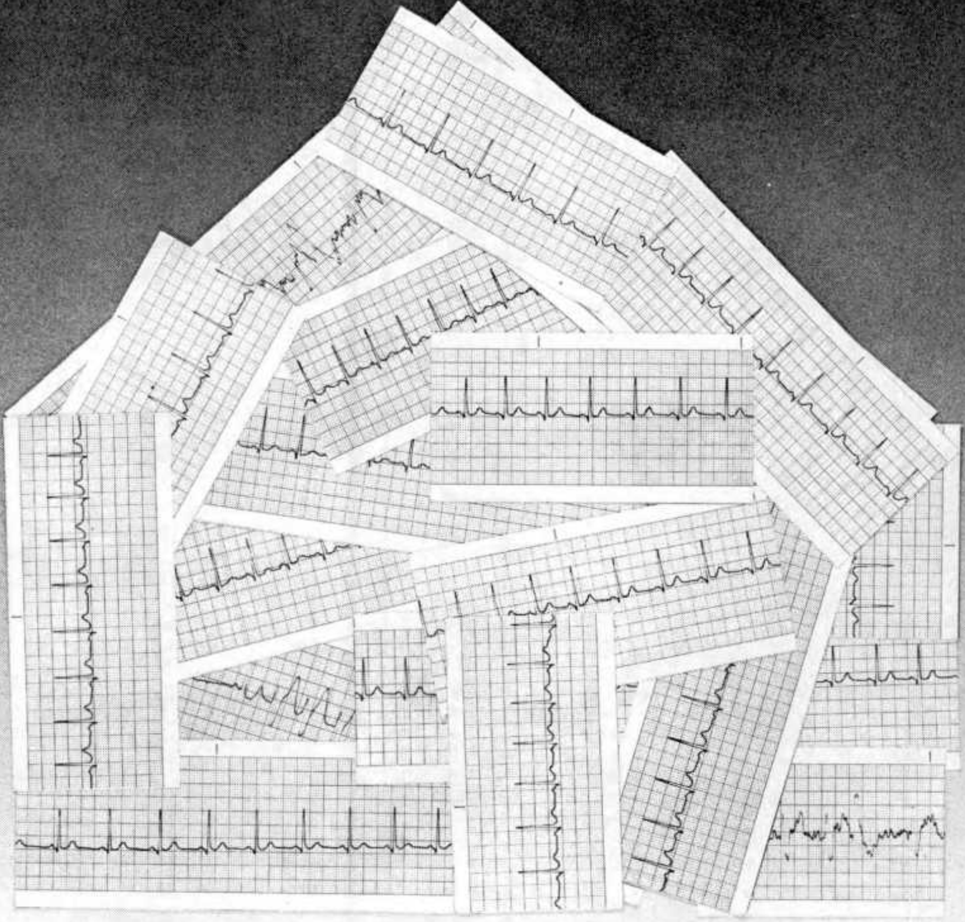
Continuous ambulatory intra-arterial records of 37 untreated hypertensive patients have confirmed the presence of a circadian rhythm of blood pressure with a nadir about 0300 hours and a slow subsequent rise which becomes steeper at the time of waking. Three groups (>5 patients each) were restudied 8 weeks after treatment with beta-adrenergic blocking drugs in conventional dosage regimens. Each reduced daytime blood pressure but the changes seen at night and in the early morning were not significant. Changing the time of dosage still did not affect the early morning rise, and it was suggested that this phase was the result of sympathetic alpha-adrenergic activity. This hypothesis was tested by giving a long-acting alpha blocking agent (indoramin 100 mg) to 9 untreated patients at 2300 hours on the second night of a 48-hour study. Comparison with the first night showed a significant reduction in blood pressure during the night and early morning, but the slope of the early morning rise was unaffected. By contrast, a study of 11 patients treated with labetolol t.i.d. abolished the early morning rise. These observations have important implications in the understanding of essential hypertension and formulation of treatment regimens.



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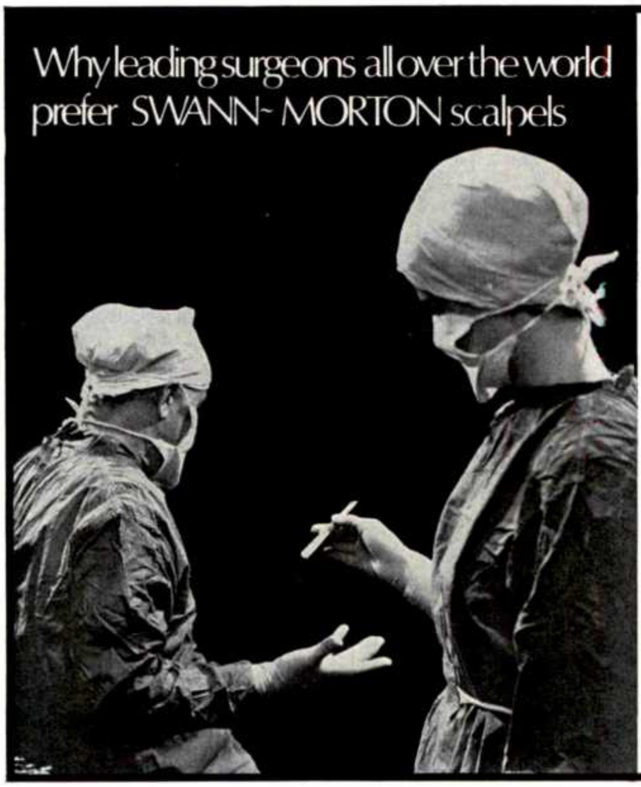
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I hereby confirm that the above mentioned doctor is a member of the junior hospital staff/ resident/intern at......................

....

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2. Acta med. scand., 119, **193**, 1973
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British Heart Journal

A monthly journal of cardiology published in association with the British Cardiac Society

Abnormal left ventricular wall movement in patients with chest pain and normal coronary arteriograms. Relation to inferior T wave changes and mitral prolapse *D. G. Gibson and D. J. Brown* 385

Echocardiographic study of significance of left ventricular minor axis shortening during pre-ejection phase of systole *P. A. N. Chandraratna, G. Vlahovich, and W. S. Aronow* 392

Echocardiographic pattern of posterior mitral valve leaflet movement after mitral valve repair *R. D. Thomas, D. A. S. Mary, and M. I. Ionescu* 399

Mitral stenosis with high left ventricular diastolic pressure *T. A. Traill, M. G. St. John Sutton, and D. G. Gibson* 405

Clinical and haemodynamic evaluation of mounted porcine heterograft in mitral position *L. Cotter and Hugh C. Miller* 412

Measuring the effect of a mobile coronary care unit upon the community *N. J. Vetter, S. Pocock, and D. G. Julian* 418

Coronary artery vasospasm: the likely immediate cause of acute myocardial infarction *H. Richard Hellstrom* 426

Correlation of ejection fraction and infarct size estimated from the total CK released in patients with acute myocardial infarction *M. Hori, M. Inoue, S. Fukui, T. Shimazu, M. Mishima, N. Ohgitani, T. Minamino, and H. Abe* 433

Patterns of haemodynamic alteration during left ventricular ischaemia in man. Relation to angiographic extent of coronary artery disease *R. A. Johnson, L. M. Zir, R. W. Harper, R. C. Leinbach, A. M. Hutter, jun, G. M. Pohost, P. C. Block, and H. K. Gold* 441

QT time in patients treated with alprenolol or placebo after myocardial infarction *G. Nyberg, A. Vedin, and C. Wilhelmsson* 452

Effects of sodium nitroprusside and phenylephrine on coronary dynamics in patients with normal left ventricular function *J. D. Stephens, R. P. Hayward, D. S. Dymond, H. Ead, L. Adams, and R. A. J. Spurrell* 456

Pulmonary hypertension and sudden death in aortic stenosis *M. M. McHenry, J. Rice, H. J. Matlof, and M. D. Flamm, jun.* 463

Comparison of cathodal, anodal, and bipolar strength-interval curves with temporary and permanent pacing electrodes *Rahul Mehra and Seymour Furman* 468

Blood volume in angina pectoris *H. Åström, and B. Jonsson* 477

Doerr's theory of morphogenesis of arterial transposition in light of recent research *Benedicto Chuaqui* 481

Gross distortion of atrioventricular and ventriculoarterial relations associated with left juxtaposition of atrial appendages. Bizarre form of atrioventricular criss-cross *E. Otero Coto, J. L. Wilkinson, D. F. Dickinson, J. J. Rufilanchas, and J. Márquez* 486

Elective aortic and mitral valve surgery in patients over 70 years of age *R. Canepa-Anson and R. W. Emanuel* 493

Angiosarcoma of the heart *Margaret Shackell, Anna Mitko, P. L. Williams, and G. C. Sutton* 498

Case reports

- Sinus node dysfunction associated with absence of right superior vena cava *A. J. Camm, D. Dymond, and R. A. J. Spurrell* 504
- A case of isolated primary chylopericardium *P. Ross, S. Joseph, and D. Walker* 508

Notices 512

British Medical Association

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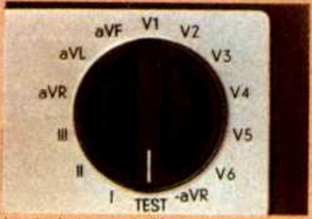

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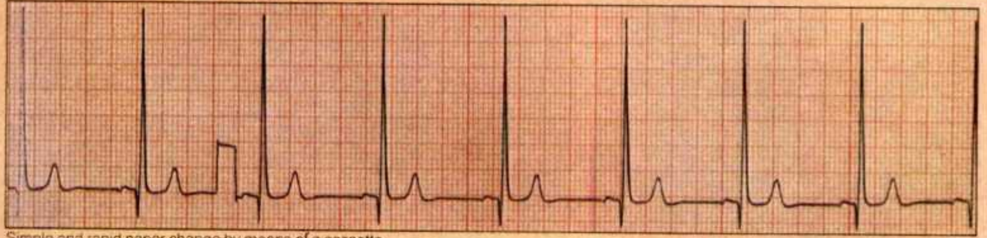

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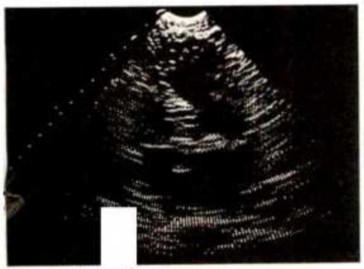

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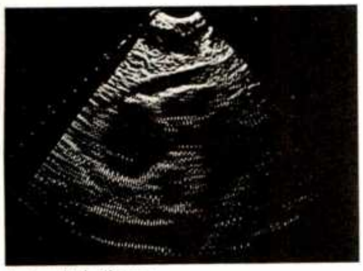

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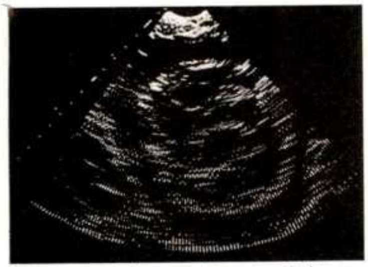

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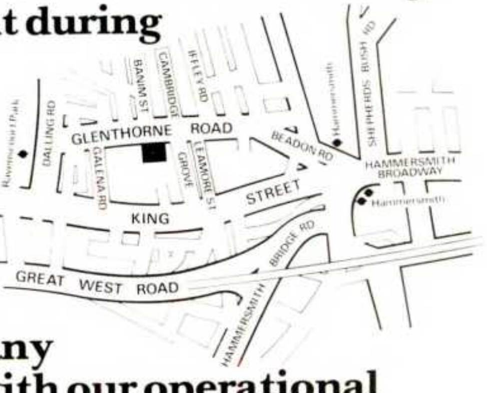

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2. JAMA (1972). 222:676.
3. New Zealand J. Med. (1972). 76:12.

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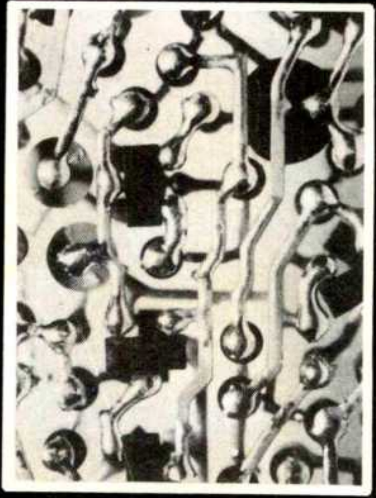

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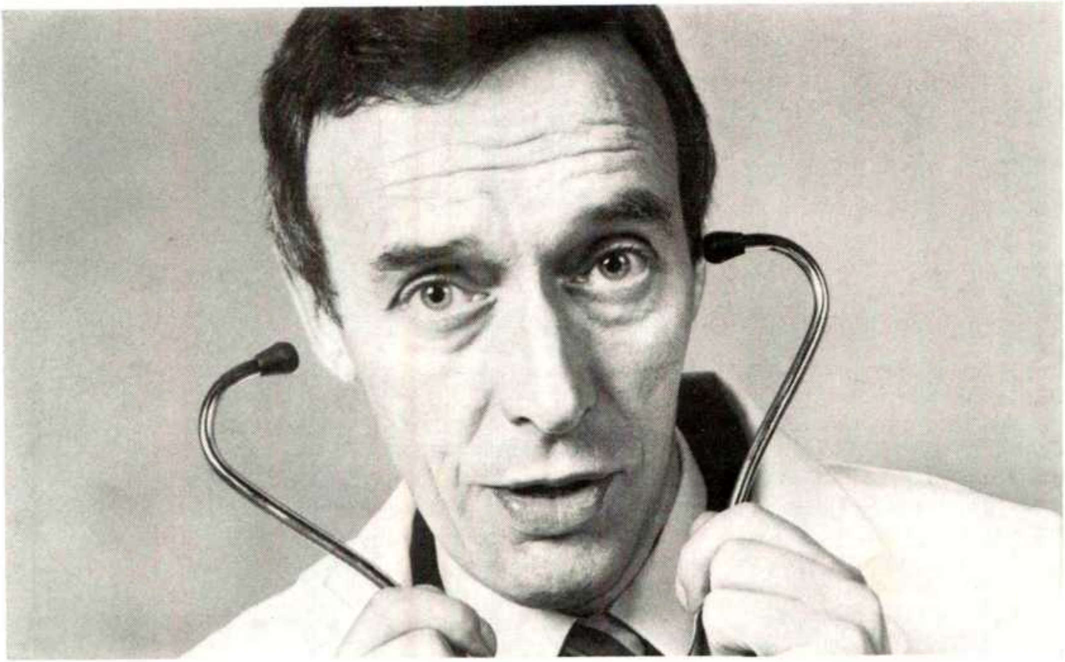

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CONTENTS

Brief Reviews: Stimulation of Cardiac Myosin Adenosine Triphosphatase in Thyrotoxicosis. *Eugene Morkin* 1

Acetylstrophanthidin-Induced Reflex Inhibition of Canine Renal Sympathetic Nerve Mediated by Cardiac Receptors with Vagal Afferents. *Marc D. Thames* 8

The Effects of Nifedipine on Acute Myocardial Ischemia and Infarction in Dogs. *Andrew P. Selwyn, Elizabeth Welman, Kim Fox, P. Horlock, Tim Pratt, and Milton Klein* 16

Effects of Inotropic and Arrhythmongenic Digoxin Doses and of Digoxin-Specific Antibody on Myocardial Monovalent Cation Transport in the Dog. *Thomas J. Hougen, Brian L. Lloyd and Thomas W. Smith* 23

Release of Active and Inactive Renin by the Porcine Kidney. *Michael D. Bailie Franz M. H. Derkx, and Maarten A. D. H. Schalekamp* 32

The Immediate Pressor Response to Saralasin in Man. A Test of Angiotensin II Receptor Vacancy. *John M. Wallace, David B. Case, John M. Laragh, Hans J. Keim, J. I. M. Drayer, and Jean E. Sealey* 38

Carotid Sinus Reflex Coronary Vasoconstriction during Controlled Myocardial Oxygen Metabolism in the Dog. *James R. Powell and Eric O. Feigl* 44

Biochemical and Morphological Correlates of Acute Experimental Myocardial Ischemia in the Dog: IV: Energy Mechanisms during Very Early Ischemia. *Jeanie M. Wood, Henry G. Hanley, Mark L. Entman, Craig J. Hartley, Julie A. Swain, Ulrich Busch, Chen-Hong Chang, Robert M. Lewis, William J. Morgan, and Arnold Schwartz* 52

Choline Uptake Into Renal Phospholipids following Renal Ischemia in Rats. *M. Barry Siegel, Leah M. Lowenstein, and Norman G. Levinsky* 62

Contribution of Prostaglandins to Muscle Blood Flow in Anesthetized Dogs at Rest, during Exercise, and Following Inflow Occulsion. *Orren Beaty III and David E. Donald* 67

The Effect of Brief Vagal Stimulation on the Isolated Rabbit Sinus Node. *Joseph F. Spear, Kenneth D. Kronhaus, E. Neil Moore, and Richard P. Kline* 75

Contractures and Increase in Internal Longitudinal Resistance of Cow Ventricular Muscle Induced by Hypoxia. *Jacek Wojtczak* 88

A Possible Role for Elastin Ligands in the Proteolytic Degradation of Arterial Elastic Lamellae in the Rabbit. *Herbert M. Kagan Paul E. Milbury Jr., and Dieter M. Kramsch* 95

The Effects of Variations in Conductivity and Geometrical Parameters on the Electrocardiograms, Using an Eccentric Spheres Model. *Yoram Rudy, Robert Plonsey, and Jerome Liebman* 104

An Analysis of the Effects of Acetylcholine on Conduction and Refractoriness in the Rabbit Sinus Node. *Eric N. Prystowsky, Augustus O. Grant, Andrew G. Wallace, and Harold C. Strauss* 112

The Relationship between Atrioventricular Nodal Refractoriness and the Functional Refractory Period in the Dog. *Michael B. Simson, Joseph Spear, and E. Neil Moore* 121

The [^{10}F]Fluorodeoxyglucose Method for the Measurement of Local Cerebral Glucose Utilization in Man. *M. Reivich, D. Kuhl, A. Wolf, J. Greenberg, M. Phelps, T. Ido, V. Casella, J. Fowler, E. Hoffman, A. Alavi, P. Som, and L. Sokoloff* 127

Instructions to Authors 138

News from the American Heart Association 141

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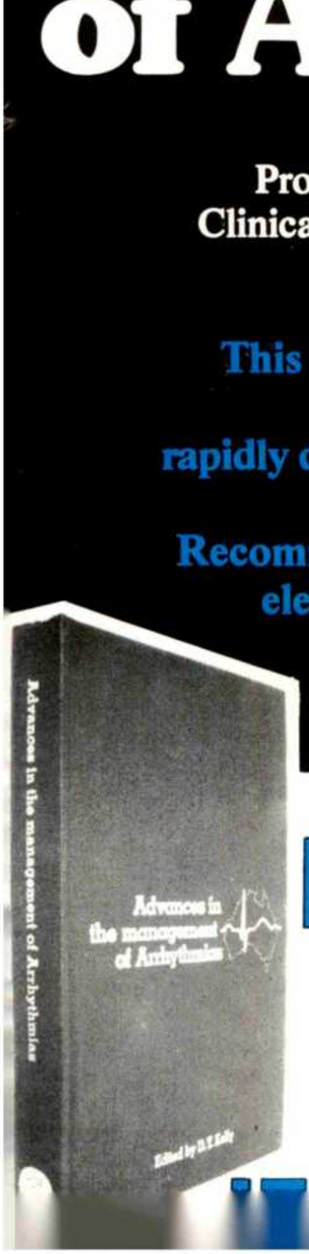
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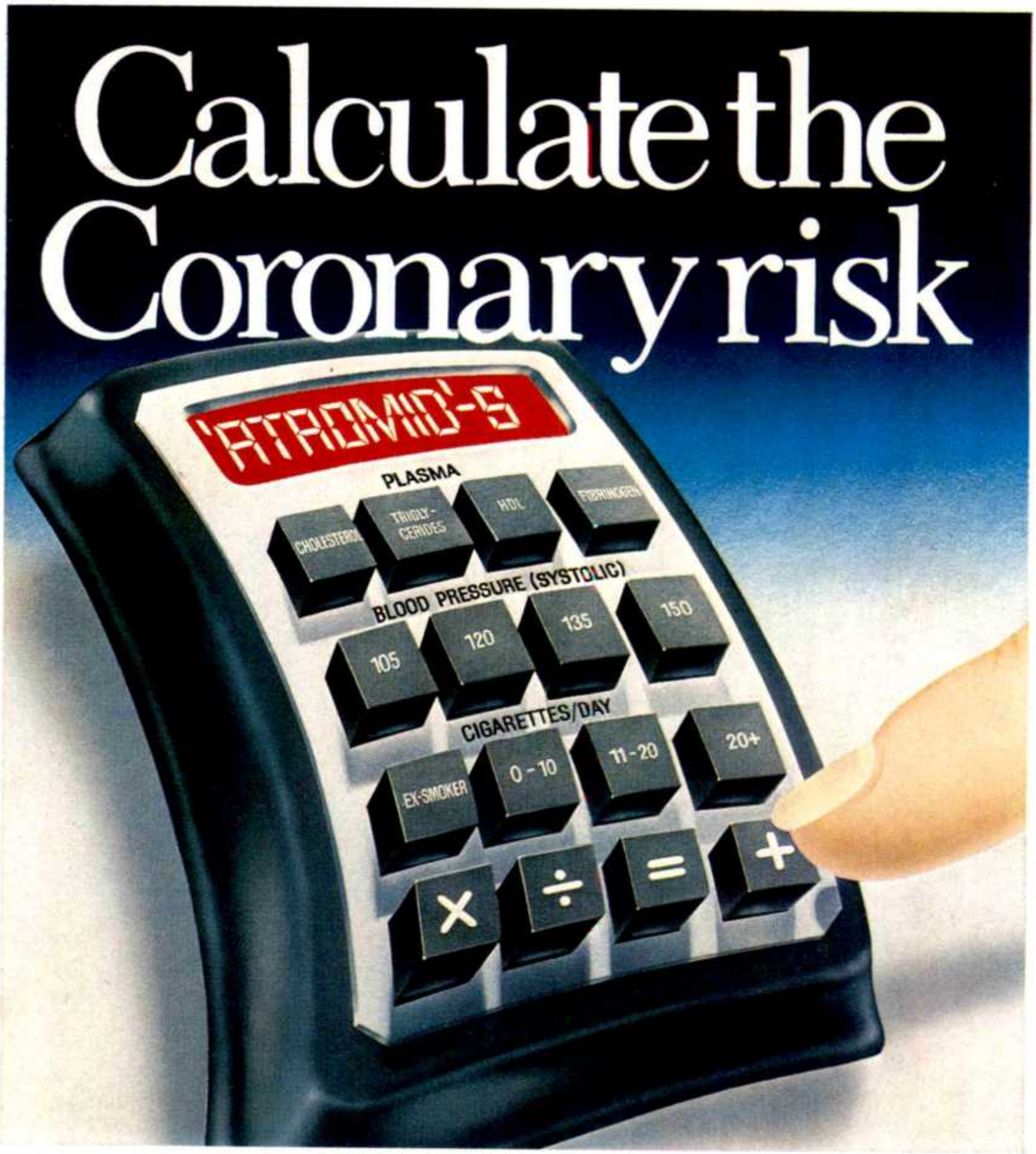

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Abnormal left ventricular wall movement in patients with chest pain and normal coronary arteriograms

Relation to inferior T wave changes and mitral prolapse

D. G. GIBSON AND D. J. BROWN

From the Cardiac Department, Brompton Hospital, London

SUMMARY Left ventriculograms of 45 patients with angina and normal coronary arteriograms were digitised frame by frame in order to detect regional abnormalities of wall movement. Though left ventricular pressures, end-diastolic volume, and ejection fraction were normal in all, regional outward movement during early systole was present in 10 patients, and abnormal inward wall movement during isovolumic relaxation also in 10, involving the apex or inferior surface. Both were present together in 8 patients, and affected segments showed normal amplitude and peak velocity of movement during ejection. These disturbances of wall movement were associated with inferior T wave changes on the electrocardiogram, and mitral prolapse, particularly when the latter resulted from delayed movement of the valve during ejection. It is suggested that the onset of contraction is delayed in affected areas, but that it proceeds normally thereafter. The resulting persistence of tension into the period of relaxation of the remainder of the ventricle may interfere locally with coronary flow, particularly during tachycardia, thus causing manifestations of regional ischaemia.

The syndrome of chest pain with normal coronary arteries is an intriguing clinical entity (Kemp *et al.*, 1967; Likoff *et al.*, 1967) since many of the features of coronary artery disease, including acute myocardial infarction, electrocardiographic abnormalities, functional mitral regurgitation, and ventricular arrhythmias may occur in the presence of normal coronary artery anatomy. Its existence demonstrates a basic lack of knowledge of the mechanisms underlying these manifestations of coronary artery disease. In a previous angiographic investigation of patients with hypertrophic cardiomyopathy (Sanderson *et al.*, 1977), it was observed that angina in this condition was associated with abnormal left ventricular relaxation. It was the purpose of the present study to examine the left ventriculograms of patients with chest pain and normal coronary arteries in greater detail than previously, in order to see if similar abnormalities were present.

Methods

Forty-five patients were studied, with normal left ventricular pressures, volumes, and coronary arteriograms. All had been referred for cardiac catheterisation on account of chest pain suspected to be caused by ischaemic heart disease. In 40, the pain was intermittent and recurrent, and was thought to represent angina pectoris. In the remaining 5, together with 5 in the preceding group, there was a history of one or more prolonged episodes of chest pain simulating that of acute myocardial infarction. In no patient was there positive electrocardiographic evidence of Prinzmetal angina.

In the history, the following features were noted: (1) the site; (2) the nature of the pain; (3) its relation to exercise or emotion; and (4) the effect of glyceryl trinitrate. These features were scored as positive (+1) if they were typical of angina pectoris, and zero if they were not. The physical findings were reviewed with special reference to third or fourth heart sounds, or systolic murmurs, particularly those suggestive of mitral regurgitation. On the electrocardiogram, the mean QRS and T vectors were measured, and the QRS-T angle derived. Any additional significant cardiographic abnormalities were noted.

Left ventriculograms were performed as previously described (Gibson *et al.*, 1976), followed by selective coronary arteriography. In all studies, the first contrast injection, apart from small test doses,

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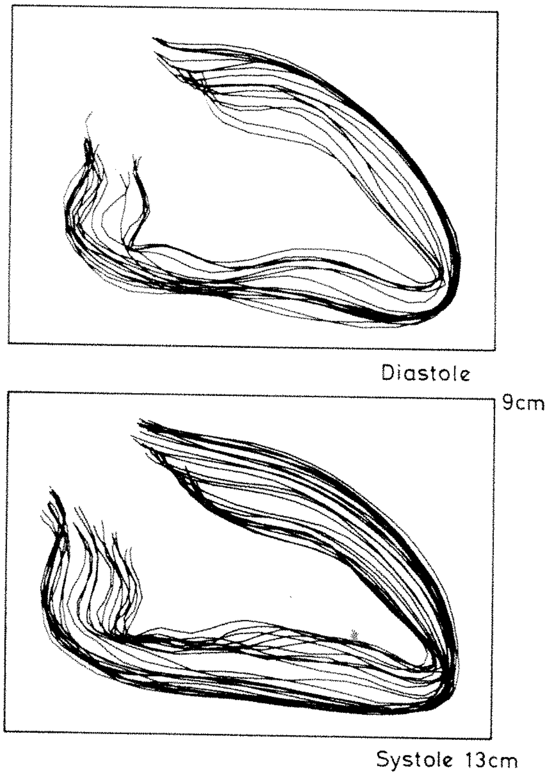

Fig. 1 *Superimposed cavity outlines from a patient with a normal coronary arteriogram showing mitral prolapse. The outlines from the start of the beat to that with the smallest area are labelled 'systole' and the remainder 'diastole'.*

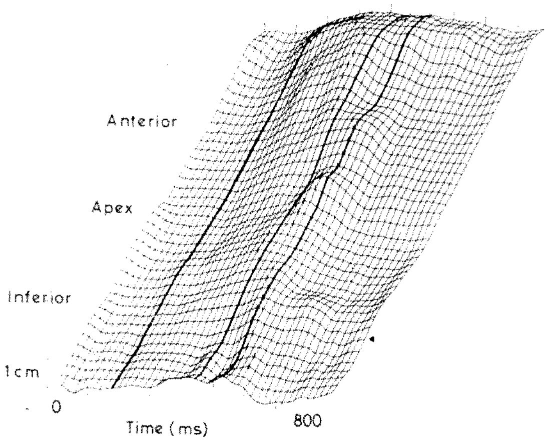

Fig. 2 *Isometric plot of a left ventriculogram, showing abnormal wall movement at the apex, where there is outward movement during early systole, and inward movement during isovolumic relaxation. The three accentuated time lines represent the onset of aortic valve opening, minimum cavity area, and the onset of mitral valve opening. The plot marked with an arrow in the inferior region represents movement of the mitral valve.*

was used for the left ventriculogram. Pressures were measured before angiography with fluid filled manometers, and were referred to the level of the mid-thorax. Left ventriculograms were digitised frame by frame (Gibson *et al.*, 1976), using a Summagraphics digitiser and a Prime 300 computer system. From digitised data, the following information was extracted.

(1) End-diastolic volume and ejection fraction.

(2) Plots of superimposed cavity outlines (Fig. 1). From these plots, regions where the overall amplitude of wall movement was reduced could be identified. In addition, an assessment of the presence or absence of mitral valve prolapse was made. The term 'prolapse' is to some extent a misnomer, since in many cases the valve did not move outward from its end-diastolic position, rather it failed to move inwards normally with the base of the heart during early and mid-ejection, and this was associated with a pronounced increase in local curvature. This sequence of events on the digitised cavity outlines was readily recognisable to a radiologist as mitral prolapse on the original angiogram (Aranda *et al.*, 1975; Smith *et al.*, 1977).

(3) Isometric plots of regional wall movement were prepared (Gibson *et al.*, 1976) (Fig. 2). The timing of the cine frames showing the start of aortic valve opening and of mitral valve opening were superimposed, along with that of the minimum cavity area. From these plots, abnormalities of wall movement during the two isovolumic periods were identified and localised.

(4) Specific plots from abnormal regions of endocardial position and its rate of change with time were made so that abnormal wall movement could be analysed in greater detail (Gibson *et al.*, 1976). These were compared with similar plots from normal regions of the same ventricle (Fig. 2). Measurements were made of overall amplitude of movement, of any outward movement before, or immediately after the start of aortic valve opening, of inward or outward movement during the interval between minimum cavity area and mitral valve opening, and, finally, of the peak rate of inward movement during ejection.

A series of similar plots showing movement in the region of the mitral valve was prepared (see Fig. 4) in order to define the events of mitral valve prolapse in more detail. From these records, measurements

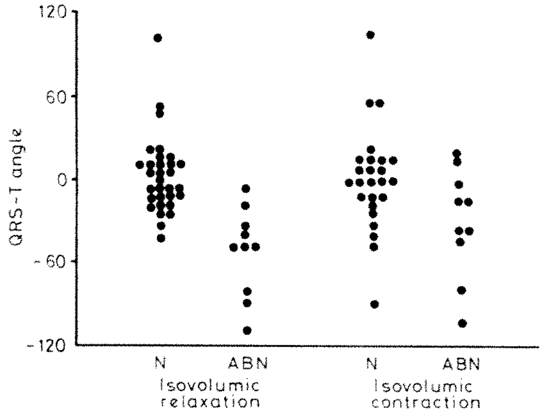

Fig. 3 *Relation between QRS-T angle and abnormal left ventricular wall movement during isovolumic contraction and relaxation.*

were made of: (a) overall amplitude of movement of the valve; (b) any outward movement (that is towards the left atrium) between the times of aortic valve opening and maximum cavity area; (c) the amplitude of inward movement between the times of minimum cavity area and mitral valve opening, expressed in absolute terms and also as a percentage of total movement.

Statistical analysis was by t tests, Fisher's exact probability tests, or χ^2 tests, as appropriate.

Results

CLINICAL

In only 5 patients were all the characteristics of angina pectoris present, and in 14 there were none (Table 1). On physical examination, a soft systolic murmur was present in 6, though none had a mid-systolic click or late systolic murmur. The latter finding reflects our belief that cardiac catheterisation is not necessary to diagnose this entity, and to this extent the series of patients studied was a selected one. No patient had clinical evidence of left ventricular disease, though 2, with left bundle-branch block, had reversed splitting of the second heart sound.

Table 1 *History of chest pain*

No features of angina pectoris	14	(0)
1 feature of angina pectoris	6	(1)
2 features of angina pectoris	12	(5)
3 features of angina pectoris	8	(2)
4 features of angina pectoris	5	(2)

Figures in parentheses indicate patients with history of prolonged chest pain simulating myocardial infarction.

Chest *x*-ray showed a normal sized heart in all cases.

ELECTROCARDIOGRAM

The electrocardiogram was abnormal in 16 patients: inferior T wave inversion, 10; left bundle-branch block, 2; left anterior hemiblock, 2; T wave inversion V1 to V5, 1; and generalised T wave flattening, 1.

No patient had significant Q waves, and all were in sinus rhythm.

HAEMODYNAMICS

Left ventricular end-diastolic pressure was less than 12 mmHg in 31 patients, and between 12 and 15 mmHg in 14.

ANGIOGRAPHY

Left ventricular end-diastolic volume was less than 140 ml in all cases, and ejection fraction was in the range 63 to 88 per cent. Significant mitral prolapse was present on inspection of the angiograms in 16 patients. Abnormal outward movement of endocardium was identified before or immediately after aortic valve opening in 10 patients (Fig. 2). In 9, the main area involved was the apex, and in 1 the inferior surface. In no case was the anterior wall affected. Studies of regional function indicated that the mean amplitude of outward wall movement during early systole was 2·3 ± 1 mm (mean ± 1 standard deviation). The overall excursion of wall movement in affected areas was 9 ± 1 mm at a peak velocity of 9·3 ± 3 cm/s. These values did not differ significantly from those of 8 ± 2 mm and 9·4 ± 3 cm/s in normal regions.

ISOVOLUMIC RELAXATION

Abnormal inward movement of endocardium was present in 10 patients, usually involving the inferior surface (8 patients), or less commonly, the apex (1) or both (1) (Fig. 2). Abnormal outward wall movement (greater than 7 mm) occurred in 12 patients, involving the anterior wall in all. Of these, 7 also showed additional inward movement during the same period, involving the inferior surface.

INTERRELATIONS OF CLINICAL FEATURES

A number of interrelations was present between abnormal left ventricular wall movement during the 2 isovolumic periods and other clinical features:

(1) The presence of inferior T wave changes on the electrocardiogram was associated with the presence of abnormal wall movement during both isovolumic periods (Fig. 3). This was significant (P < 0·01).

Table 2 *Relation between isovolumic abnormalities and mitral prolapse*

(A) Isovolumic contraction abnormalities	*Mitral prolapse Present*	*Absent*
Present	8	2
Absent	8	27
(B) Isovolumic relaxation abnormalities	*Mitral prolapse Present*	*Absent*
Present	5	5
Absent	11	24

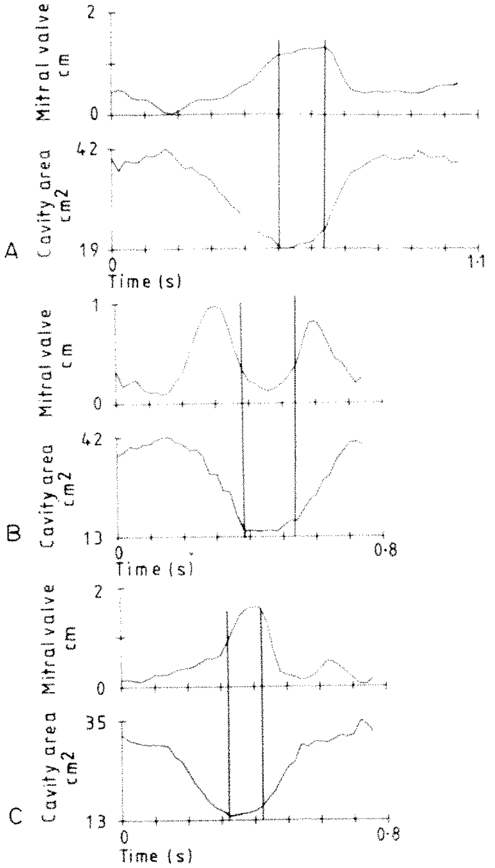

Fig. 4 *(A) Selective plot of mitral valve movement in comparison with changes in left ventricular cavity area. The two vertical lines represent the timing of minimum cavity area and mitral valve opening. Upward displacement of the mitral valve trace represents movement of the valve towards the left ventricular cavity. The greater part of valve movement occurs during ejection rather than during isovolumic relaxation. (B) Selective plot of mitral valve movement, showing mid-systolic prolapse of the valve into the left atrial cavity. Layout as Fig. 4A. (C) Selective plot of mitral valve movement, showing delay during ejection, and inward movement occurring mainly during isovolumic relaxation. Layout as Fig. 4A.*

(2) Abnormalities of isovolumic contraction and relaxation were both present in 8 patients.

(3) Mitral valve prolapse, defined simply as failure of the mitral valve to move inwards in systole, along with the appearance of increased local curvature, determined by direct inspection of angiograms, was present in 16 patients and was associated with the presence of abnormalities of isovolumic contraction (Table 2). In an attempt to analyse this movement in more detail, plots of mitral valve movement were used. In all patients, maximum inward movement of the valve towards the left ventricular cavity occurred at the time of mitral valve opening, followed by outward movement during filling. However, during systole, 3 separate patterns of movement could be defined:

(a) (30 patients). In the majority of patients, the greater part of inward movement occurred during ejection. Between the time of minimum cavity area and mitral valve opening, further inward movement was usually seen, but its amplitude was small (Fig. 4A).

(b) (4 patients). In these patients, inward movement began normally after aortic valve opening, but during mid-ejection there was abrupt outward movement of the valve into the left atrial cavity, which reversed during relaxation. This pattern appeared to represent classical mid-systolic prolapse of the mitral valve (Fig. 4B).

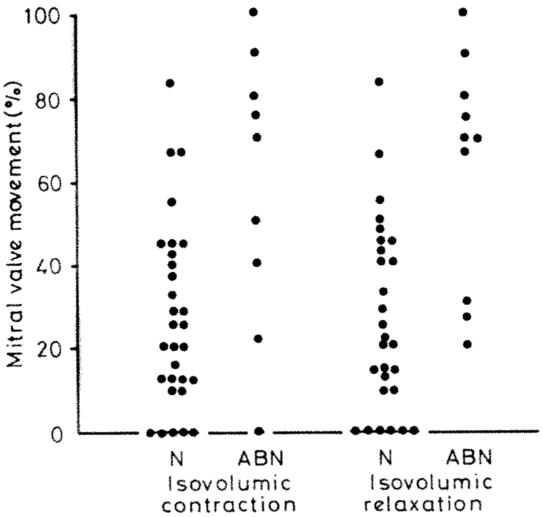

Fig. 5 *Relation between mitral valve movement and abnormal left ventricular wall movement during isovolumic contraction and relaxation. Mitral valve movement is expressed in terms of the percentage of the total amplitude over the cardiac cycle occurring during isovolumic relaxation.*

(c) (11 patients). In these patients, the greater part of inward movement of the mitral valve occurred between the times of minimum cavity area and mitral valve opening, that is during isovolumic relaxation. A discontinuity in the rate of inward movement was consistently seen 20 to 40 ms before the time of minimum cavity area (Fig. 4C).

The relation of these abnormalities of mitral valve movement to those of the ventricular wall is shown in Fig. 5. This shows that abnormal wall movement during either of the two isovolumic periods is associated with the condition of 45 per cent or more of total inward movement of the valve occurring during isovolumic relaxation. There was no relation between abnormal wall movement and mid-systolic prolapse in the 4 patients in whom it was present.

(4) The nature of the chest pain: it was not possible to demonstrate any connection between the nature of the pain and the electrocardiogram, the presence of mitral prolapse, or disturbances of left ventricular wall movement.

Discussion

In the present study we have suggested that regional differences in timing in wall movement occur in patients who present with chest pain and normal coronary arteries, and in whom standard measures of left ventricular function are normal. Proving this contention is difficult since the ventriculograms of patients of this type are often used as a standard of comparison against which those of patients with more clearly defined pathology are judged. However, other objective abnormalities, including inferior T wave changes and mitral valve prolapse, have been described in similar populations of patients with chest pain and normal coronary arteries (Dwyer *et al.*, 1969; Kemp *et al.*, 1973). In this study, inward movement of the apex or inferior surface of the ventricle during isovolumic relaxation was closely associated with inferior T wave changes on the electrocardiogram, and this relation was specific to this particular abnormality and did not occur with left anterior hemiblock or left bundle-branch block. Though angiographic criteria for the diagnosis of mitral prolapse are not precise, even the qualitative definition used in this study showed a significant association between prolapse and incoordinate wall movement. More detailed analysis indicated that this association was with a specific type of valve motion. The close relation between two independent and objective abnormalities, namely T wave changes and mitral valve prolapse and areas of incoordinate behaviour of the left ventricle, is strong evidence that the detection of such areas is not the result of artefact introduced by the method used to analyse the angiograms, so that they should be considered abnormal.

The disturbance of isovolumic contraction closely resembled that seen in patients with coronary artery disease (Gibson *et al.*, 1978). Outward wall movement started before aortic valve opening, and continued for the first 40 to 60 ms of ejection. The wall then moved inward, with normal amplitude and velocity, but relaxation in these regions was delayed in 9 out of 11 with respect to other parts of the same ventricle. This type of movement is compatible with the idea that the onset of contraction is delayed in affected areas, but that it proceeds normally thereafter. Abnormalities of isovolumic relaxation were also similar to those seen in coronary artery disease (Gibson *et al.*, 1976), with inward movement of endocardium in one area being associated with outward movement elsewhere to maintain cavity volume constant during the period between aortic valve closure and mitral valve opening. Unlike the distribution seen in coronary artery disease, inward movement during isovolumic relaxation occurred only at the apex and along the inferior surface, so that compensatory movement involved the free wall. These abnormalities of movement are thus very similar to those previously described by a number of authors in patients with mitral valve prolapse accompanied by mid-systolic click and late systolic murmur. These have included delayed inferior relaxation, which may be of such an extent as to cause the development of a two-chambered left ventricle, and also premature outward movement along the anterior wall of the cavity occurring in late systole or early diastole (Grossman *et al.*, 1967; Ehlers *et al.*, 1970; Jeresaty, 1971; Liedtke *et al.*, 1973; Scamperdonis *et al.*, 1973). In these patients, also, coronary arteriography is usually normal in spite of a history of anginal pain and the presence of electrocardiographic abnormalities suggesting local ischaemia (Pocock and Barlow, 1970a).

Several types of mitral valve movement were seen in the present study. One abnormal pattern appeared to correspond with mitral prolapse defined echocardiographically, with abrupt backward movement of the valve into the left atrium during mid-systole (Fig. 4B). In our patients, this was not consistently associated with either a mid-systolic click and late systolic murmur or with abnormal wall movement. By contrast, the second type of abnormality, movement downward during isovolumic relaxation rather than during ejection, was frequently associated with abnormal movement at the apex or along the inferior wall. This type of movement did not simply reflect that of the base of the heart, since it was not associated with any consistent change in long axis. It is thus unlikely to have been caused by any functional disturbance of longitudinally directed fibres of the ventricular wall, but rather it is the behaviour that would be predicted if there were a delay in the onset of papillary muscle contraction similar to that occurring in the wall. In a further 8 patients, a local increase in mitral valve curvature occurred in the absence of any abnormality of timing. Patients with mitral valve prolapse, therefore, do not seem to be a homogeneous group, and studies of the timing of mitral valve movement may shed further light on this confusing syndrome.

Patients with chest pain and normal coronary arteries may thus present with a variety of interrelated clinical features, for which we offer the following explanation. A primary feature appears to be regional delay in the onset of contraction involving the apex, inferior wall, or papillary muscles, possibly caused by local delay in activation since contraction then proceeds normally in affected areas. The reason for this specificity of site is unknown, but it also occurs in patients with coronary artery disease (Gibson *et al.*, 1978). Since the duration of contraction is normal, delay in the onset of tension is associated with its persistence in affected areas into the period of isovolumic relaxation. Coronary flow, particularly in subendocardial regions (Gregg and Fisher, 1963; Kirk and Honig, 1964), occurs almost exclusively in diastole, so that the combination of persisting tension and a short filling period such as occurs with tachycardia might lead to regional ischaemia. Evidence for myocardial ischaemia occurring during stress testing comes from studies showing lactic acid production (Neill *et al.*, 1968; Bemiller *et al.*, 1973; Kemp *et al.*, 1973; Boudoulas *et al.*, 1974) or the development of perfusion abnormalities (Korhola *et al.*, 1977). Once local ischaemia developed, then relaxation would be further prolonged as occurs experimentally during reperfusion (Tyberg *et al.*, 1974). This would tend to aggravate the interference with coronary flow, leading to the development of angina or even myocardial infarction (Campeau *et al.*, 1968; Greenberg and Dwyer, 1974). The combination of activation delay and local ischaemia might predispose to the development of ventricular arrhythmias, particularly during and immediately after exertion, of the type described by previous authors (Pocock and Barlow, 1970b; Gooch *et al.*, 1972) in patients with mitral valve prolapse.

Although wall motion abnormalities were seen in a proportion of our patients, in 28, or almost two-thirds, left ventriculography was totally normal. Previous comparison between PA and lateral views (Gibson *et al.*, 1976) makes it unlikely that a significant number of patients with abnormal movement in the isovolumic periods was missed by using single plane angiography. It seems, therefore, that patients with chest pain and normal coronary arteriograms are not a homogeneous population, but that a single subgroup appears to consist of those in whom wall motion abnormalities, mitral prolapse, and T wave changes occur together.

The present results nevertheless have implications for the definition of standards for the assessment of wall movement using ventriculography. Records taken from patients such as we have described are frequently assumed to be normal, though we have given reasons for supposing that in an appreciable number this may not be the case. In the short term, we suggest that patients with mitral prolapse or electrocardiographic abnormalities should be excluded from such studies. In the longer term, one possible approach might be to correlate angiographic studies more closely with noninvasive techniques by which truly normal subjects can be investigated.

The computing equipment used in this study was provided by the DHSS as part of its experimental programme.

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Echocardiographic study of significance of left ventricular minor axis shortening during pre-ejection phase of systole

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SUMMARY This study was designed to investigate the changes in dimensions of the left ventricular minor axis that occur during the pre-ejection period of systole. Three groups of subjects were studied: 29 normal subjects (group 1); 16 patients with mitral regurgitation and 2 patients with ventricular septal defect (group 2); 11 patients with left ventricular volume overload (excluding those with mitral regurgitation and ventricular septal defect), 10 with aortic regurgitation, and 1 with arteriovenous fistula (group 3). To define the onset of left ventricular contraction (mitral valve closure), the electrocardiogram and mitral valve echocardiogram were recorded, and to establish the onset of ejection (aortic valve opening), the electrocardiogram and aortic valve were recorded at a paper speed of 50 mm per second, with 40 ms time lines. The left ventricular echogram and electrocardiogram were then recorded, and the dimensions of the left ventricular minor axis at the onset of contraction and of ejection were measured. In group 1 the dimension of the left ventricular minor axis either did not change (14 subjects) or increased by 1 to 2 mm (15 subjects) during the pre-ejection period. In group 2, the dimension of the left ventricular minor axis decreased in all the subjects during the pre-ejection period (mean = 3 mm). The decrease in the dimension was the result of posterior motion of the interventricular septum during the pre-ejection period; there was no anterior motion of the posterior wall until the onset of ejection except in 1 patient. In group 3 there was no change in the dimension of the left ventricular minor axis during the pre-ejection period except in 1 patient whose dimension increased by 2 mm. We conclude that shortening of the dimension of the left ventricular minor axis during the pre-ejection period occurs in mitral regurgitation and ventricular septal defect, but not in normal subjects or patients with other forms of left ventricular volume overload which are not accompanied by loss of left ventricular volume into another cardiac chamber during the pre-ejection phase of systole. Left ventricular minor axis shortening during the pre-ejection period should be a useful adjunct to the echocardiographic diagnosis of mitral regurgitation and ventricular septal defect.

Conflicting results have been obtained by investigators who have studied the changes that occur in the left ventricular minor axis dimension during the pre-ejection phase of systole (Rushmer, 1954; Karliner *et al.*, 1971; Vokonas *et al.*, 1973). The experimental studies of Rushmer indicated that there was an increase in minor axis diameter during isovolumic contraction (Rushmer, 1954). Vokonas and associates studied the dynamic geometry of the left ventricle with left ventricular cineangiography (Vokonas *et al.*, 1973). They observed that there was no significant change in transverse axis dimension during isovolumic contraction. This investigation was designed to study the changes in echocardiographic left ventricular minor axis dimensions during the pre-ejection phase of systole, (i) in normal subjects, (ii) in subjects with mitral regurgitation and ventricular septal defect, and (iii) in patients with other forms of left ventricular volume overload who do not have a loss of left ventricular blood into another cardiac chamber in systole.

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Subjects and methods

The patients were in the supine or left lateral decubitus position during the echocardiographic examination. An Ekoline 20 ultrasonoscope, a 2·25 MHz 10 cm focus 0·5 in transducer, and Honeywell 1856 or Irex recorder were used. The echocardiograms were recorded at a paper speed of 50 mm/s, with 40 or 100 ms time lines.

The left ventricular echocardiogram (with clear delineation of the left septal and left ventricular posterior wall endocardial echo) was recorded using standard techniques. The left ventricle was recorded at the level of the chordae tendineae, except in a 6-month-old baby on whom the recording was made at the level of the mitral leaflets (since this is the standard position for infants). The echocardiogram of the anterior and posterior leaflets of the mitral valve was then recorded, after which echoes from the aortic valve were obtained.

The time interval (QMC) from the Q wave of the electrocardiogram to coaptation of the mitral leaflets was measured. Hirschfeld and co-workers (1976) demonstrated that the coaptation of mitral leaflets occurred at the point of rapid increase in left ventricular pressure. Hence the onset of contraction could be defined by measuring the QMC interval. The time interval from the Q wave of the electrocardiogram to aortic valve opening (Q-Ao) was used to determine the onset of ejection. Left ventricular internal dimension was measured at the point of onset of contraction (Fig. 1). Measurements of mitral valve closure, aortic valve opening, and left ventricular dimensions were made at similar RR intervals from 5 separate complexes and average values obtained. It should be noted that beat-to-beat variation of the QMC and Q-Ao interval at similar RR intervals was small (about 5 ms). The change in minor axis dimension during the pre-ejection phase of left ventricular contraction equals the dimension at the onset of contraction minus the dimension at the onset of ejection. (The pre-ejection phase of contraction is the same as isovolumic systole for normal subjects but in patients with mitral regurgitation there may be no isovolumic systole; therefore the former term was used.)

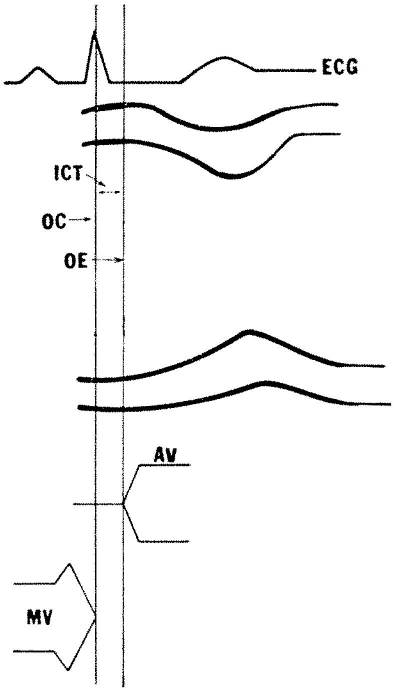

Fig. 1 *Diagrammatic representation of the left ventricle, aortic valve (AV), and mitral valve (MV). Mitral closure occurs at the onset of left ventricular contraction (OC), and onset of ejection (OE) occurs at the time of aortic valve opening. ICT = isovolumic contraction time.*

In 2 patients (one with severe mitral regurgitation and another with severe aortic regurgitation) simultaneous left ventricular echograms and central aortic pressure (using a micromanometer-tipped catheter) were recorded at paper speeds of 50 and 100 mm/s and 40 ms time lines.

Three groups of patients were studied. Group 1 comprised 29 normal subjects whose ages ranged from 20 to 40 years. There were 12 women. Group 2 comprised 18 patients with left ventricular volume overload who had loss of left ventricular volume into another cardiac chamber (right ventricle or left atrium) during the pre-ejection phase of systole; 16 had mitral regurgitation documented by left ventricular cineangiography and 2 had uncomplicated ventricular septal defects with left-to-right shunts (QP:QS of 2·8 and 3, respectively). All the patients with mitral regurgitation had moderate (grade 3/4) or severe (grade 4/4) regurgitation, except case 14 who had grade 1/4 regurgitation and case 13 who had grade 2/4 reflux. Group 3 consisted of 10 patients with moderate or severe aortic regurgitation as assessed by aortic root angiography and 1 patient with a fistula between the left iliac artery and vein (after laminectomy). These patients had types of left ventricular overload which were not associated with loss of left ventricular blood into another cardiac chamber during the pre-ejection period.

Results

The results are outlined in Tables 1, 2, and 3. The data from normal subjects are shown in Table 1. The left ventricular minor axis dimensions at the onset of contraction (mitral valve closure) ranged from 36 to 54 mm. The minor axis dimension at the onset of ejection ranged from 37 to 54 mm. None of the normal subjects showed shortening of the minor axis dimension during the pre-ejection period. Fourteen patients did not exhibit a change in minor axis dimension during the pre-ejection phase of systole. The diameter of the minor axis increased by 1 to 2 mm in 15 subjects. Data from patients with mitral regurgitation and ventricular septal defect are given in Table 2. All 16 patients with mitral regurgitation showed minor axis shortening during the pre-ejection period. Shortening of the minor axis diameter during the pre-ejection period was the result of posterior motion of the interventricular septum (range 2 to 4 mm); there was no anterior motion of the left ventricular posterior wall except in 1 patient. The percentage minor axis shortening during the pre-ejection period ranged from 3·3 to 7·2 per cent, with a mean of 5·5 per cent.

Data obtained from patients with aortic regurgita-

Table 1 *Echocardiographic data in normal subjects*

Case no.	*Age (y)*	*Sex*	*DOC*	*DOE*	*△D-PEP*
1	25	F	42	43	−1
2	22	F	38	38	0
3	23	F	45	45	0
4	24	M	54	54	0
5	26	M	46	47	−1
6	29	M	54	54	0
7	25	F	37	38	−1
8	25	M	46	48	−2
9	24	M	41	41	0
10	26	M	48	50	−2
11	21	F	40	40	0
12	22	M	49	49	0
13	23	M	44	44	0
14	20	F	48	48	0
15	27	F	42	42	0
16	22	M	49	49	0
17	38	F	46	47	−1
18	32	M	48	48	0
19	22	F	39	40	−1
20	40	F	52	52	0
21	25	F	46	47	−1
22	20	F	36	37	−1
23	31	M	52	54	−2
24	29	M	47	49	−2
25	33	M	50	51	−1
26	23	M	48	48	0
27	21	M	51	52	−1
28	31	M	45	47	−2
29	25	M	39	40	−1

DOC, left ventricular minor axis dimension in mm at the onset of contraction; DOE, left ventricular minor axis dimension in mm at the onset of ejection; △ D-PEP = DOC − DOE, that is change in minor axis dimension during the pre-ejection phase of systole. A negative value signifies an increase in minor axis diameter during the pre-ejection period.

Table 3 *Aortic regurgitation*

Case no.	*Age*	*Sex*	*DOC*	*DOE*	*△D-PEP*
1	32	M	72	72	0
2	41	F	58	58	0
3	42	M	57	57	0
4	44	M	68	68	0
5	52	M	60	60	0
6	31	M	75	75	0
7	27	M	59	61	−2
8	17	M	67	67	0
9	76	F	60	60	0
10	52	M	63	63	0
Arteriovenous fistula					
1	36	M	57	57	0

Table 2 *Echocardiographic data in mitral regurgitation and in ventricular septal defect*

Case no.	*Age*	*Sex*	*DOC*	*DOE*	*△D-PEP*	*D-IVS-PEP*	*DPW-PEP*	*%MAS-PEP*
Mitral regurgitation								
1	40	M	62	58	4	4	0	6·4
2	22	F	68	64	4	4	0	5·8
3	26	M	67	63	4	4	0	5·9
4	17	M	70	67	3	3	0	4·2
5	52	F	55	51	4	4	0	7·2
6	37	F	58	54	4	4	0	6·8
7	40	F	61	57	4	4	0	6·5
8	56	M	65	61	4	4	0	6·1
9	18	M	74	71	3	3	0	4·0
10	47	F	60	57	3	3	0	5·0
11	53	F	54	51	3	3	0	5·5
12	31	F	55	52	3	3	0	5·4
13	52	M	53	50	3	2	1	5·6
14	30	F	42	40	2	2	0	4·7
15	38	F	60	58	2	2	0	3·3
16	54	M	58	55	3	3	0	5·2
Ventricular septal defect								
1	1½	F	23	21	2	2	0	
2	6 mth	M	28	25	3	3	0	

D-IVS-PEP, posterior displacement (in mm) of the interventricular septum during the pre-ejection phase of systole; DPW-PEP, anterior displacement of the left ventricular posterior wall endocardial echo during the pre-ejection phase of the systole. %MAS-PEP, percentage minor axis shortening during the pre-ejection phase of systole $= \frac{\triangle D - PEP}{DOC} \times 100$.

tion or arteriovenous fistula are shown in Table 3. All except 1 patient showed no change in minor axis diameter during the pre-ejection phase of systole.

The left ventricular echocardiogram of a normal subject is illustrated in Fig. 2. The minor axis dimension at the onset of ejection is 1 mm greater than that at the onset of left ventricular contraction. The ultrasound recording of a patient with mitral regurgitation is depicted in Fig. 3. The minor axis diameter at the onset of contraction is 6·0 cm and that at the onset of ejection is 5·7 cm, indicating that there has been minor axis shortening of 3 mm during the pre-ejection phase of systole. An echocardiogram of the left ventricle and a simultaneous recording of the central aortic pressure (catheter tip micromanometer) in a patient with mitral regurgitation are presented in Fig. 4. There is posterior motion of the septum resulting in minor axis shortening before the upstroke of the aortic pressure pulse. A left ventricular echocardiogram from a 6-month-old baby with a ventricular septal defect is illustrated in Fig. 5. Minor axis shortening in the pre-ejection phase of systole is evident.

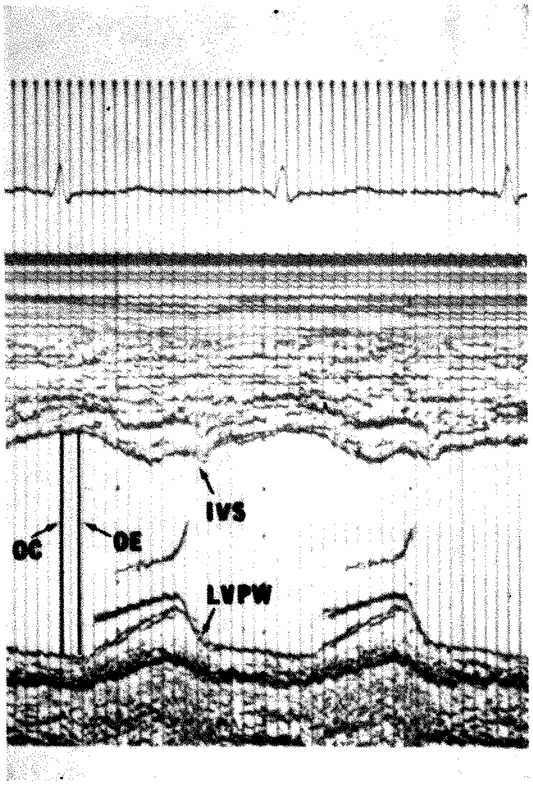

Fig. 2 *Echocardiogram of the left ventricle in a normal subject. The minor axis dimension at the onset of contraction (OC) is 46 mm, and that at the onset of ejection (OE) is 47 mm. The minor axis diameter has increased by 1 mm during the pre-ejection phase of systole.*

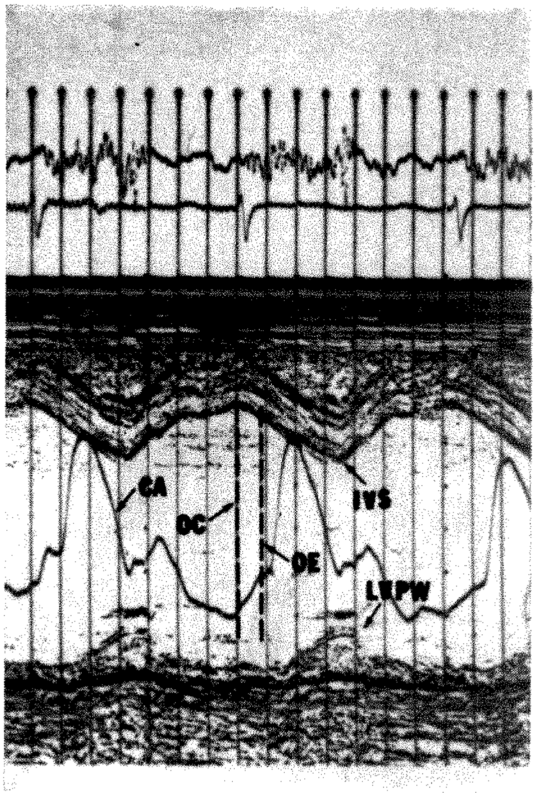

Fig. 3 *Echocardiogram of left ventricle from a patient with mitral regurgitation. The left ventricular minor axis diameter is 60 mm at the onset of contraction, and 57 mm at the onset of ejection. The minor axis has shortened by 3 mm during the pre-ejection phase of systole. A carotid pulse (CA) recording was also made in this patient. Note that the onset of the carotid upstroke occurs later than the onset of ejection (as determined by point of aortic valve opening) because of the delay in transmission of the carotid pulse. IVS, interventricular septum; LVPW, left ventricular posterior wall. The time lines are 100 ms apart. The vertical dotted line OC indicates the timing of the onset of ventricular contraction (not the minor axis dimension, since the line does not extend from the left septal endocardium to the endocardium of the posterior wall), and the line OE indicates the onset of left ventricular ejection.*

Discussion

Left ventricular dilatation with increased excursion of the septum, left atrial dilatation, increased pulsa-

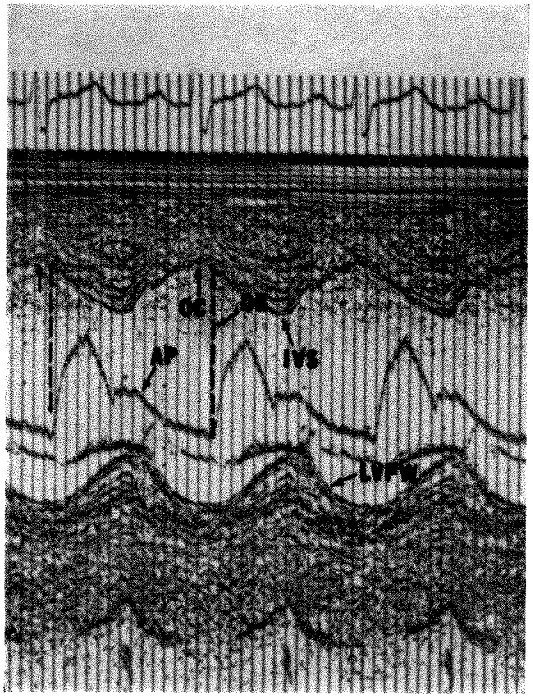

Fig. 4 *Simultaneous recording of the left ventricular echocardiogram and aortic pressure (AP) recorded by means of a catheter-tipped micromanometer placed just above the aortic valve in a patient with mitral regurgitation. Note that posterior motion of the septum has occurred before the onset of the upstroke of the aortic pressure pulse (onset of ejection), indicating minor axis shortening in the pre-ejection phase of systole. OC, onset of contraction; OE, onset of ejection. Time lines are 40 ms apart.*

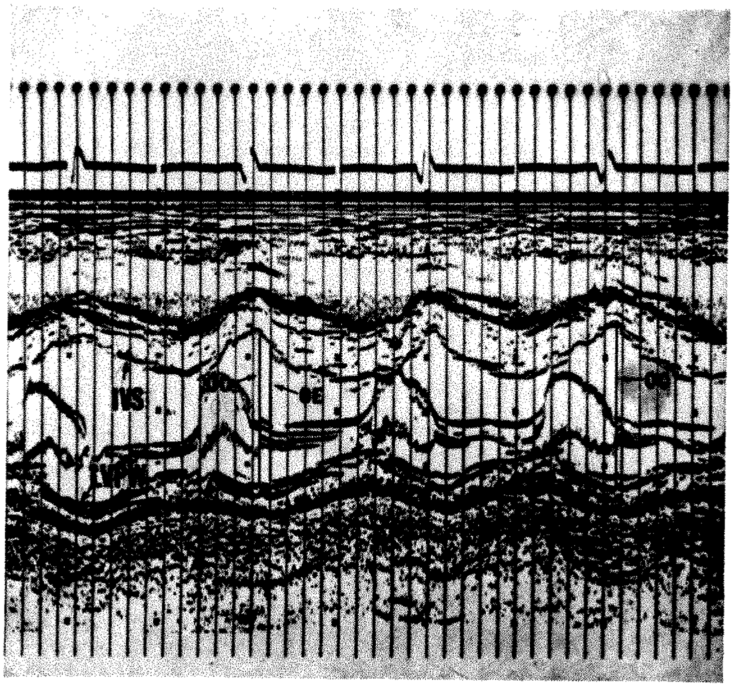

Fig. 5 *Ultrasound recording of the left ventricle in a 6-month-old baby with a ventricular septal defect. The minor axis dimension at the onset of contraction (OC) is 28 mm, and that at the onset of ejection (OE) is 25 mm. Thus a 3 mm shortening of the minor axis diameter has occurred before the onset of ejection. The time lines are 40 ms apart.*

tion of the left atrial posterior wall, and increased E-F slope of the mitral valve have been noted in the echocardiograms of patients with mitral regurgitation (Feigenbaum, 1976). Many of these ultrasound features may also be seen in other conditions such as aortic regurgitation, arteriovenous fistula, and persistent ductus arteriosus which produce left ventricular volume overload. We, therefore, explored the value of echocardiographically detectable minor axis shortening during the pre-ejection period as a means of differentiating between mitral regurgitation or ventricular septal defect, which are conditions associated with loss of left ventricular blood into another cardiac chamber during the pre-ejection period, and other forms of left ventricular volume overload that do not exhibit left ventricular volume loss in the pre-ejection phase of systole.

Several investigators have studied the dimensional changes in the left ventricle during isovolumic contraction. Though an increase in minor axis diameter during isovolumic contraction has been reported in dog experiments, recent studies in animals and man have failed to confirm this finding (Rushmer, 1954; Karliner *et al.*, 1971; Vokonas *et al.*, 1973). Rankin and associates (1976) indicated that this discrepancy arose because the dynamic geometry of the left ventricle in the open chested dog preparation was different from that in conscious subjects. They pointed out that ventricular volume diminished during thoracotomy, and the tendency of the ventricle to assume a more spherical shape during isovolumic contraction was increased. Karliner and colleagues (1971) noted a mean decrease in transverse diameter of 1 mm before aortic valve opening in 6 subjects without left ventricular dysfunction. Three of their subjects had organic heart disease, 2 had functional cardiac murmurs, and 1 had atypical chest pain. Vokonas and associates (1973) found no significant changes in left ventricular minor axis dimension of normal subjects, while in patients with mitral regurgitation and good left ventricular function the transverse axis shortened an average of 5·2 per cent during the pre-ejection phase of left ventricular contraction. We observed that the left ventricular minor axis in normal subjects either did not change or increased slightly (1 to 2 mm) during the pre-ejection period. In contrast, minor axis shortening during the pre-ejection period was noted in all our patients with mitral regurgitation. Venco and associates (1977) noted a reduction in left ventricular minor axis dimensions during the upstroke of the apex cardiogram in patients with mitral regurgitation, reflecting backward movement of blood into the left atrium before aortic valve opening. It is of interest that the mean value of 5·2 per cent for transverse axis shortening during the pre-ejection period in a group of patients with compensated mitral regurgitation reported by Vokonas and co-workers (1973) is similar to that observed (5·5%) in our study. Minor axis shortening during the pre-ejection period was also observed in 2 patients with ventricular septal defect who had left-to-right shunts. It is possible that patients who have only right-to-left shunting (Eisenmenger ventricular septal defect) may not show minor axis shortening in the pre-ejection period. Patients with other forms of left ventricular volume overload, who did not have a 'run-off' of left ventricular blood into another cardiac chamber in systole, did not exhibit pre-ejection minor axis shortening.

The diagnosis of mitral regurgitation is critical in certain situations. Patients with severe acute aortic regurgitation secondary to infective endocarditis show premature mitral valve closure, which to a certain extent prevents transmission of the high left ventricular diastolic pressure to the left atrium (Morganroth *et al.*, 1977). The ocurrence of mitral regurgitation in such a patient will, therefore, result in severe haemodynamic deterioration (Morganroth *et al.*, 1977). The early detection of mitral regurgitation in that situation is of paramont importance. Serial echocardiograms to detect minor axis shortening before aortic valve opening will be of value in this setting.

Certain factors may limit the usefulness of pre-ejection minor axis shortening as an index of mitral regurgitation or ventricular septal defect. This echographic sign may not be present in patients who have late systolic mitral regurgitation. It is conceivable that some patients who have abnormal septal motion caused by left bundle-branch block, anteroseptal myocardial infarction, or idopathic hypertrophic subaortic stenosis may not exhibit posterior septal motion in the pre-ejection period, in spite of the presence of significant mitral regurgitation. Vokonas and co-workers (1973) observed that changes in geometry before ejection were less evident in patients who had mitral regurgitation and poor left ventricular performance. Since all our patient had good left ventricular function, the usefulness or limitation of minor axis shortening in the pre-ejection period as a sign of mitral regurgitation in patients with decompensated left ventricles remains to be established. Two patients in our group had mild mitral regurgitation. The role of echocardiography in detecting minor axis shortening during the pre-ejection period in patients with mild mitral regurgitation needs further investigation.

In summary, left ventricular minor axis dimension either does not change or increases slightly during the pre-ejection phase of systole in normal subjects and in patients with forms of left ventricular volume overload which are not accompanied by loss of left ventricular volume into another cardiac chamber during the pre-ejection period. In contrast, patients with mitral regurgitation and ventricular septal defect have minor axis shortening in the pre-ejection phase of systole. Echocardiographic left ventricular minor axis shortening in the pre-ejection period should prove to be a valuable adjunct in the diagnosis of mitral regurgitation and ventricular septal defect.

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Announcement

Basic cardiology seminar

A seminar on basic cardiology will be organised every year by the French Society of Cardiology and sponsored by the European Society.

The first session will be held on 25, 26, and 27 October 1979, at Merck, Sharp & Dohme-Chibret Laboratories Centre, 63000 Clermont-Ferrand (France). It will include two topics: haemodynamic exploration in cardiology, and heart and calcium.

The objective is to establish a dialogue between experts and young cardiologists who want to improve their knowledge of experimental and/or clinical, basic, and/or applied research. The seminar will be bilingual, French-English. Registration and hotel accommodation will be free of charge.

Applicants must: (a) be less than 35 years old; (b) have a perfect knowledge of French or English; (c) submit a file including: professional training, hospital and university titles, a list of publications, and a reference from the department head.

Applications will be received until 15 May 1979. The number of participants is limited to 90.

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Echocardiographic pattern of posterior mitral valve leaflet movement after mitral valve repair

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SUMMARY The pattern of movement of the posterior leaflet at the time of opening of the stenosed mitral valve has been described as either anterior or posterior in direction.

In 32 patients who underwent mitral annuloplasty, the anatomical features of the mitral apparatus were correlated with the postoperative echocardiographic pattern of movement of the posterior leaflet. Anterior movement of the posterior leaflet was associated with extensive disease of this leaflet, and posterior movement with minimal disease. No relation was found between valve orifice or anterior leaflet mobility and the pattern of movement of the posterior leaflet.

One of the earliest applications of echocardiography was in the diagnosis of mitral valve disease (Edler and Gustafson, 1957). Among the diagnostic criteria now used, emphasis is placed on the pattern of movement of the posterior leaflet during mitral valve opening. When the posterior leaflet moves in an anterior direction, that is parallel to the anterior leaflet, this is considered to indicate mitral stenosis, in contrast to the normal mitral valve where the two leaflets move in opposite directions (Duchak *et al.*, 1972; McLaurin *et al.*, 1973; Cope *et al.*, 1975). However, while anterior movement of the posterior leaflet is accepted as a reliable sign to rule out the presence of a normal mitral valve, posterior movement of this leaflet has been reported in patients with mitral stenosis (Levisman *et al.*, 1975). This finding imposes limitations on the use of pattern analysis in the diagnosis of mitral stenosis.

The mechanism of this contrasting pattern of posterior leaflet movement is not known. Factors such as commissural adhesion, shortening of the chordae tendineae, or mobility of the posterior leaflet or the mitral ring have been implicated (Duchak *et al.*, 1972; Levisman *et al.*, 1975; Feigenbaum, 1976; Henry and Kastl, 1977). In the present report, the echocardiographic appearance of the posterior leaflet has been studied in patients after mitral annuloplasty. This surgical procedure allows direct assessment of the valve apparatus, and the operative findings help to explain the different patterns of movement.

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Patients and methods

Echocardiographic studies of both mitral valve leaflets were performed in 32 consecutive patients immediately after, and at varying intervals, for a period of up to 1 month, after mitral annuloplasty. The patients comprised 24 women and 8 men, with an age range from 19 to 66 years (mean 45 years).

The aetiology of mitral valve disease was rheumatic in 28 patients, congenital in 2, and degenerative in 2. Twelve of the 28 patients had pure or predominant mitral regurgitation and 16 had mixed mitral valve disease. All the patients had open mitral annuloplasty (Wooler *et al.*, 1962), the indications for which have been previously described (Mary *et al.*, 1973). In addition to mitral annuloplasty, one patient required plication of the posterior leaflet and one closure of an atrial septal defect. Six other patients had tricuspid annuloplasty and 7 had aortic valve replacement.

At operation the condition of the posterior leaflet was classified into 2 categories. Firstly, minimal disease, in which the leaflet was either normal, minimally thickened, or only thickened at the commissures, and with retained pliability. Secondly, extensive disease, in which the leaflet was thickened and fibrosed with impaired pliability. After mitral annuloplasty a direct estimate of the anatomical dimensions of the mitral valve orifice was made and this was expressed in relation to body surface area as previously described (Mary *et al.*, 1973).

Echocardiography was performed using a Smith-

Kline Ekoline 20 ultrasonoscope and a 2·25 MHz transducer focused at 10 cm, and recorded by Polaroid photography or with a Cambridge multichannel strip chart recorder. By angulating the transducer, M-mode sector scans were obtained at different sagittal planes through the mitral valve, from the base of the heart to the apex (Feigenbaum, 1972). At the level of the mitral valve, a transverse scan was performed to cover a wide area of the mitral leaflets. In all patients distinct echoes were obtained from the anterior and posterior leaflets and the latter was always separated from the mitral valve ring. The diastolic closure rate (EF slope—measured as the EF$_0$ slope) and amplitude of excursion of the anterior leaflet (CE amplitude) were obtained from recordings where these values were greatest (Edler, 1967). An average of at least 4 cardiac cycles was used.

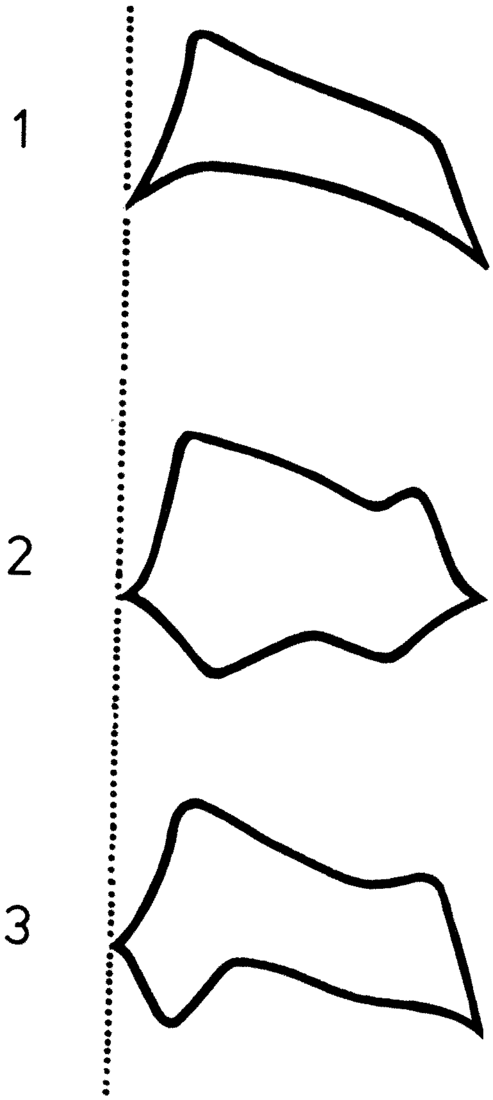

Fig. 1 *Diagram of the 3 patterns of posterior leaflet movement after mitral annuloplasty*

Results

In the 32 patients studied 3 patterns of movement of the posterior leaflet were observed (Fig. 1). These patterns were type 1, in which the initial movement of the posterior leaflet, at the time of valve opening, was in the same direction as the anterior leaflet. In types 2 and 3, the initial movement of the posterior leaflet was in a direction opposite to that of the anterior leaflet. Because we were assessing the initial movement in this study, types 2 and 3 were grouped together as posterior movement of the posterior leaflet.

Analysis of these echocardiographic patterns was performed by an independent observer without knowledge of the surgical details of the mitral apparatus. There was no difference in the pattern of the leaflet movement when recorded by both Polaroid photography and on a strip chart.

Anterior movement of the posterior leaflet was observed in 25 patients and posterior movement in the remaining 7 patients (Table). These patterns were analysed according to the condition of the posterior leaflet and the dimensions of the mitral valve orifice obtained at surgery, and the EF slope and anterior leaflet amplitude. In 6 out of 7 patients in whom the posterior leaflet moved in a posterior direction (Fig. 2 and 3), the leaflet had minimal disease, in contrast to the 25 patients with an anterior movement (Fig. 4) of whom 20 had a posterior leaflet with extensive disease. This difference was significant ($P < 0·01$ Fisher's exact test). These relations were still significant when the 4 patients with congenital or degenerative mitral valve disease were excluded from the analysis ($P < 0·05$).

Table *Surgical and echocardiographic data in 32 patients after mitral annuloplasty*

Pattern of leaflet movement	*No. of patients*	*Valve orifice at surgery (mm/m^2)*	*Valve amplitude (mm)*	*EF slope (mm/s)*
Anterior	25*	21 ± 0·6	23 ± 1·1	46 ± 3·5
Posterior	7†	21 ± 1·9	24 ± 1·8	71 ± 11·0

Results expressed as mean ± standard error of the mean.
*One with non-rheumatic disease.
†Three with non-rheumatic disease.

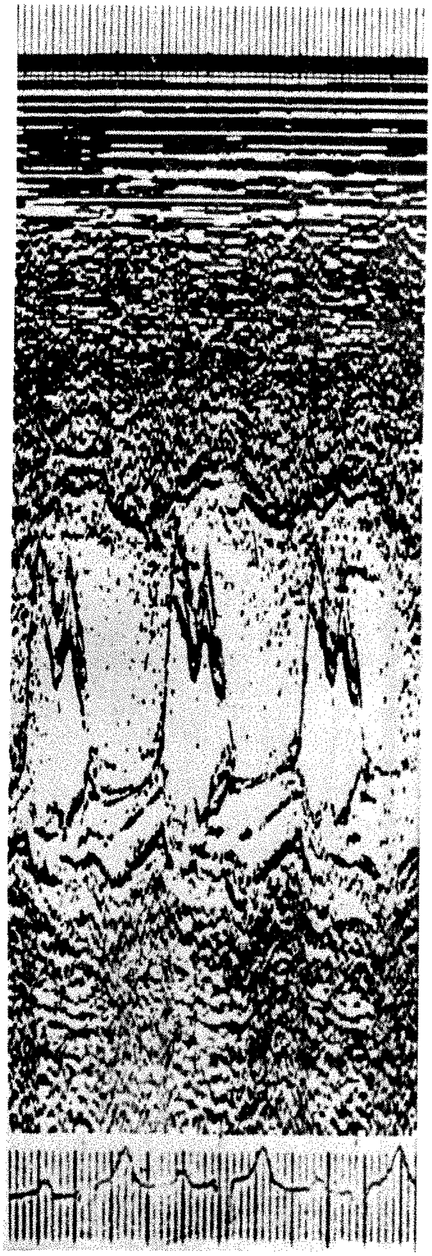

Fig. 2 *Echocardiogram from a patient with posterior movement of the posterior leaflet (pattern 2).*

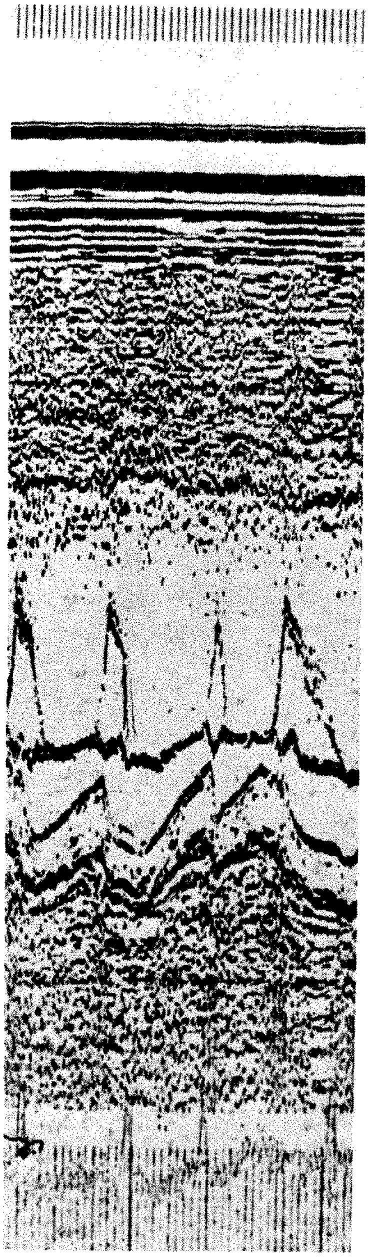

Fig. 3 *Echocardiogram from a patient with posterior movement of the posterior leaflet (pattern 3).*

The rheumatic and non-rheumatic patients have been grouped together in the analysis because the mean dimension of the mitral valve orifice, anterior leaflet amplitude, and EF slope were essentially the same. There was no significant difference in dimension of the mitral valve orifice or anterior leaflet amplitude between the 2 types of valve movement (Table). The mean (± SEM) EF slope obtained from echocardiograms of patients with a posterior movement was signifi-

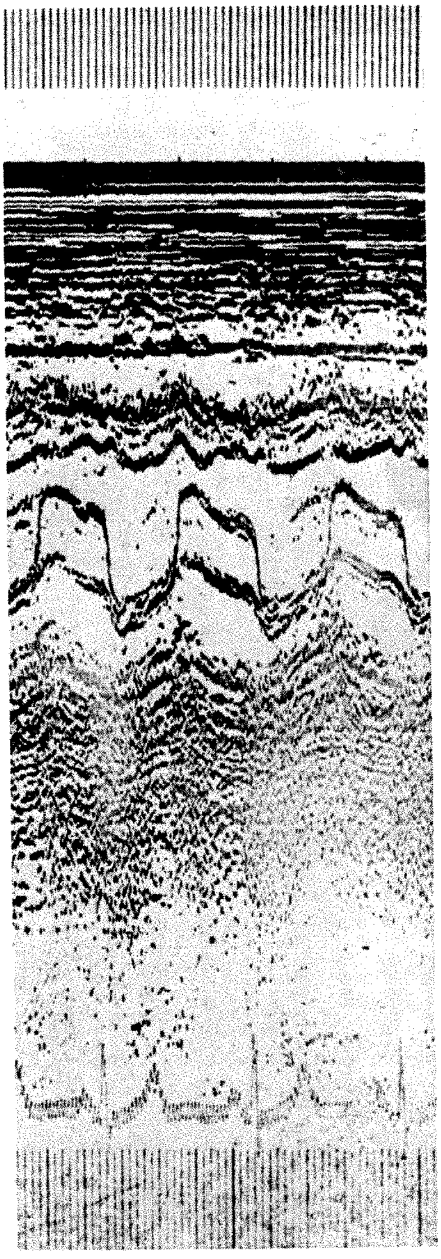

Fig. 4 *Echocardiogram from a patient with anterior movement of the posterior leaflet (pattern 1).*

cantly faster (71 ± 11·0 mm/s) than that seen in patients with anterior movement (46 ± 4·0 mm/s) ($P < 0·05$). Significance was assessed by Bailey's modification of Student's t test (Bailey, 1959).

Discussion

Analysis of the pattern of movement of the anterior mitral valve leaflets with echocardiography was introduced by Edler and Gustafson (1957). Reduction of the EF slope of the anterior leaflet remains an essential feature in the diagnosis of mitral stenosis (Edler, 1967). Investigation into the mechanism of movement of the anterior leaflet soon established that the EF slope was determined by the rate of left ventricular filling and movement of the mitral valve ring (Moreyra *et al.*, 1969; Layton *et al.*, 1973; Mary *et al.*, 1973; Laniado *et al.*, 1975). A reduction was therefore found to occur in conditions in which the cardiac output or the rate of ventricular filling was reduced, as well as in mitral stenosis (McLaurin *et al.*, 1973; Quinones *et al.*, 1974).

However, pattern analysis of the posterior leaflet movement continues to be of value in the diagnosis of mitral stenosis. Duchak *et al.* (1972) studied the direction of movement of the posterior leaflet at the time of mitral valve opening and found that in mitral stenosis the posterior leaflet moved anteriorly. This was in contrast to the posterior movement seen with a normal mitral valve, whether or not the EF slope was reduced. These patterns of movement of the posterior leaflet were observed by other investigators who concluded that posterior movement excluded the diagnosis of mitral stenosis (Feigenbaum, 1972; Teichholz, 1975). However, posterior movement was subsequently reported in patients with mitral stenosis (Berman *et al.*, 1975; Cope *et al.*, 1975; Flaherty *et al.*, 1975; Levisman *et al.*, 1975; Ticzon *et al.*, 1975; Feigenbaum, 1976; Henry and Kastl, 1977). A controversy therefore exists in the use of analysis of the pattern of movement of the posterior leaflet, and this is partly because the underlying mechanism is unexplained. One of the problems in defining the mechanism stems from the unreliability of echocardiography in assessing the thickness of mitral leaflets (Raj *et al.*, 1976). An estimate of thickening of the posterior leaflet, with resulting impairment of mobility, forms an essential part in any study to explain the pattern of leaflet movement. Patients with mitral annuloplasty were selected for study because the anatomy of the mitral valve can be directly examined during the operation. In addition, the surgical procedure, aimed at correcting the regurgitation, achieves this by producing commissural fusion, a feature common to all types of mitral stenosis. This operation was therefore used to investigate the relation of possible anatomical mechanisms to the echocardiographic pattern of movement.

Several mechanisms have been suggested to explain the abnormal posterior leaflet movement. Duchak *et al.* (1972) and Levisman *et al.* (1975) proposed that anterior movement of the posterior leaflet was dependent on the movement of the whole mitral apparatus, particularly the mitral ring. Feigenbaum (1976) and Henry and Kastl (1977) suggested that such movement was the result of commissural fusion which pulls the posterior leaflet in a direction similar to that of the anterior leaflet. These suggested mechanisms include the basic assumption that the mobility of the posterior leaflet is so impaired by thickening or fibrosis that movement of any of its parts follows the movement of the commissure or the annulus. The only hypothetical mechanism given to explain a posterior movement in mitral stenosis is that the posterior leaflet is still flexible and mobile (Berman *et al.*, 1975; Levisman *et al.*, 1975).

The present investigation has allowed a direct test of the hypothesis that movement of the posterior leaflet, shown by echocardiography, is basically determined by the pliability and mobility of the leaflet. The results have shown that a posterior movement was associated with a thin and mobile posterior leaflet and anterior movement was more frequently associated with extensive disease of the posterior leaflet. The absence of a significant difference in anterior leaflet amplitude between anterior and posterior movement was not unexpected, since a pliable anterior leaflet was a necessary prerequisite for annuloplasty (Wooler *et al.*, 1962). This finding makes it unlikely that posterior movement is dependent on the presence of a reduced anterior leaflet movement as suggested by Henry and Kastl (1977). We found an increased EF slope in the group of patients with posterior movement, but Levisman *et al.* (1975) showed that 5 out of 54 patients with severe mitral stenosis had posterior movement. Though our patients are not strictly comparable with those of Levisman *et al.* (1975), it appears that a pliable posterior leaflet can exist in mitral stenosis regardless of the severity of the stenosis.

While anterior movement of the posterior leaflet excludes a normal mitral valve, the results in this study have shown that posterior movement cannot rule out the diagnosis of mitral stenosis. The findings in the study do not exclude a role for commissural fusion or valve ring mobility in anterior movement. However, the pattern of movement in the centre of the posterior leaflet, through which the ultrasound beam is directed, appears to be determined by the pliability of that leaflet.

Addendum

As this manuscript was being submitted we read the paper of Shiu *et al.* (1978). These authors have confirmed that posterior movement of the mitral leaflet occurs in mitral stenosis. In addition, they reported that this pattern of movement tended to occur in patients with less severe stenosis, though not exclusive of this, and that at operation greater mobility of both leaflets was found. It is not clear how the latter finding was assessed.

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Mitral stenosis with high left ventricular diastolic pressure

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SUMMARY Three patients with mitral stenosis are described, in whom the haemodynamic findings at cardiac catheterisation were more suggestive of left ventricular myocardial disease, in that the left ventricular diastolic pressure was high and the mitral valve gradient small. However, their echocardiograms showed abnormal wall movement during diastole characteristic of severe inflow obstruction, with slow and protracted filling, and at operation mitral stenosis was confirmed. Left ventricular wall stress was estimated throughout the cardiac cycle in one patient, and the diastolic stress-strain relation shown to be abnormal. The effects of mitral stenosis on left ventricular function are complex, and are not explicable simply by reduction in size of the mitral orifice.

It has been said that 'the fundamental hemodynamic expression of mitral stenosis is the presence of an elevated left atrioventricular filling pressure gradient' (Braunwald *et al.*, 1955). Therefore, in patients with this lesion in whom there is doubt as to its severity, whether because of the paucity of physical signs or because of the suspicion of left ventricular disease, it may be helpful to measure such a gradient by cardiac catheterisation.

In recent years, echocardiography has made it possible to assess the anatomical state of the valve. The signs of rheumatic involvement are broadening of the cusp echoes signifying thickening, forward movement in diastole of the posterior cusp, which indicates cusp fusion, reduced amplitude of movement when the valve or chordae are particularly rigid, and slow early diastolic closure. However, to judge the extent of physiological disturbance, it is more satisfactory to estimate the degree of obstruction to left ventricular filling from the rate of separation of the endocardial surfaces of the posterior left ventricular wall and the left side of the septum measured continuously throughout diastole (Gibson and Brown, 1973). This technique has been used to demonstrate both reduction in peak rate of filling, and disturbance of its normal pattern.

The result has been that in some cases where both cardiac catheterisation and echocardiography have been performed, the results have been discordant. We report 3 such patients in whom catheter results were such as to suggest left ventricular disease by virtue of a high left ventricular end-diastolic pressure and small mitral valve gradient, whereas the echocardiogram was diagnostic of severe disorganisation of the valve and slow left ventricular filling. They all underwent successful surgery.

Methods

ECHOCARDIOGRAPHY

Echocardiograms were recorded with the patients semi-supine and partially rotated to the left. A Smith-Kline ultrasonoscope was used and the permanent record made direct on to Polaroid film or with a Cambridge Instruments strip-chart recorder.

The records were digitised for computer processing as described by Gibson and Brown (1973) and Upton *et al.* (1976). Continuous plots were obtained of transverse left ventricular dimension, its rate of change, and instantaneous mitral leaflet velocity (Fig. 1). The normal (mean ± standard deviation) peak diastolic rate of change of dimension is 16 ± 3 cm/s; in a group of patients with unequivocal mitral stenosis this was reduced to 3 to 11 cm/s. In normal subjects most filling occurs in the first third of diastole, the rate of wall separation declining to 20 per cent of its peak value within 115 ± 20 ms, but with mitral stenosis this pattern is changed for there is no distinct rapid filling phase and dimension continues to increase at almost its peak rate throughout diastole. The peak rate of early diastolic mitral valve closure is 130 to 370 mm/s in normal subjects,

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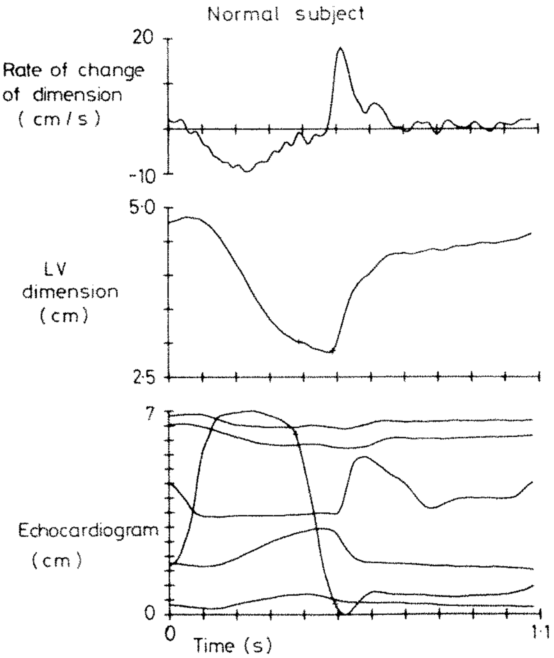

Fig. 1 *Normal subject: plots of left ventricular cavity dimension and its rate of change derived from the digitised echocardiogram reproduced in the lowest panel. The apex cardiogram is superimposed. The crosses mark times of aortic valve closure and mitral opening.*

and is reduced to below 80 mm/s in most patients with mitral stenosis.

CARDIAC CATHETERISATION

Patients were studied fasting and at rest after pre-medication with 200 mg amylobarbitone given orally one hour before. Fluid filled catheters were used with Bell and Howell transducers for the routine pressure measurements, which were referred to zero taken at the 'mid-chest', that is the mid-point of a vertical line between the sternal angle and the top of the patient table. The static accuracy of the system is assessed as within 2 per cent, and the frequency response is flat to 10 Hz. Left atrial pressure was measured directly by transseptal puncture in case 1, and as the pulmonary capillary ('wedge') pressure in the others. Zero and calibration were re-checked at the time of recording simultaneously the left ventricular and left atrial pressures. All the pressure records were taken before injection of angiographic dye. When estimating the mitral valve gradient the wedge pressure record was advanced so as to line up the 'y' descent with the fall in left ventricular pressure. In case 2, in whom left ventricular stress analysis was performed, left ventricular pressure was also measured using a Millar catheter tip micromanometer and recorded simultaneously with an echocardiogram. The results were analysed as described by Gibson and Brown (1974). Cardiac index was estimated by the direct Fick method. Assumed values for oxygen uptake were taken from Robertson and Reid (1952).

Case 1

A South African Asian woman was investigated at Brompton Hospital at the age of 41. She had rheumatic fever as a child, and at the age of 22, having been asymptomatic for a year, she had a closed mitral valvotomy, with good effect. She had uneventful pregnancies when she was 28 and 31, but when she was 36, coinciding with the onset of atrial fibrillation, she began again to notice breathlessness on exertion and tiredness. At about the same time she had a left axillary embolus. Over the succeeding years her state worsened and 4 years later, when she was admitted for investigation, she was breathless on minor exertion, NYHA grade 3, and orthopnoeic.

She was thin and dyspnoeic on the least effort. The heart rate was 80/min in atrial fibrillation. The peripheral pulses were of small volume and the arterial pressure was 110/80 mmHg. The jugular venous pressure was raised to the angle of the jaw with prominent systolic pulsation, and the liver was enlarged, pulsatile, and tender. There was clinical right ventricular hypertrophy and the first heart sound was palpable. The pulmonary closure sound was accentuated and there was a short, quiet (grade 1/4) mitral diastolic murmur, but no opening snap. There were no adventitious sounds over the lungs or peripheral oedema.

The chest *x*-ray film showed moderate increase in overall heart size, with enlargement of the left atrium and prominent upper lobe veins. The electrocardiogram confirmed atrial fibrillation and showed right ventricular hypertrophy.

The echocardiogram (Fig. 2) showed mitral valve thickening, cusp fusion—the posterior cusp moved forward in diastole—and reduction of the peak mitral diastolic closure rate to 22 mm/s. The peak rate of separation of the endocardial surfaces of the septum and posterior left ventricular wall was reduced to 6 cm/s, and the pattern of dimension increase was typical of mitral stenosis (Fig. 3).

The results obtained at cardiac catheterisation are displayed in the Table. There was pulmonary hypertension and the left atrial pressure was raised. However, there was no diastolic gradient between left atrium and ventricle as the two pressures were identical throughout diastole. The end-diastolic pressure was 28 mmHg. The left atrial V wave was 42 mmHg, but there was no mitral regurgitation

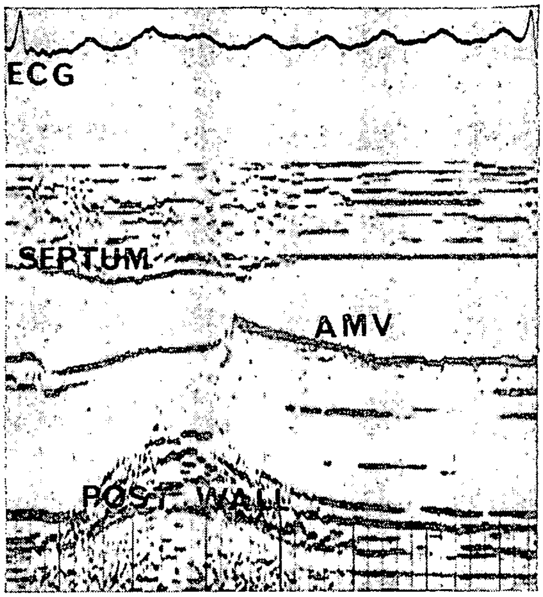

Fig. 2 *Case 1: echocardiogram showing the endocardium of the posterior side of the ventricular septum, the posterior wall, and the anterior cusp of the mitral valve (AMV).*

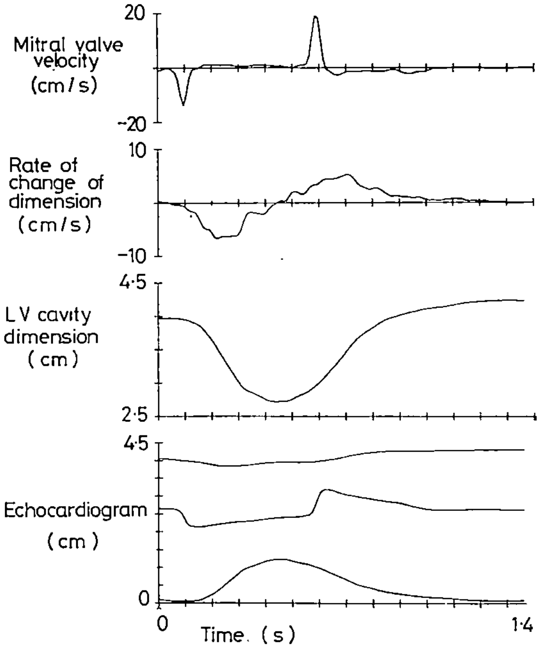

Fig. 3 *Case 1: plots from the digitised echocardiogram showing, from below upwards, the original echocardiogram, the left ventricular dimension, its rate of change, and the rate of change of position of the anterior mitral valve cusp.*

demonstrable on cineangiography.

The catheterisation findings suggested that there was no mitral valve disease, but she was referred for surgery because of the echocardiogram, and at operation was found to have thickened mitral leaflets with a small orifice. The valve was excised and replaced with a No. 3M Starr-Edwards prosthesis. Two years after operation she reports normal exercise tolerance and no orthopnoea or fatigue.

Case 2

An English housewife was aged 39 at the time of investigation. She had chorea at the age of 11 and first developed symptoms of heart disease during the first of her pregnancies, which were when she was 23, 27, and 31. During each she was breathless on exertion. When she was 35, having again become breathless and developed haemoptysis and paroxysmal nocturnal dyspnoea, closed mitral valvotomy was performed with good initial relief of her symptoms. In the next few years, however, she deteriorated again and she was readmitted for investigation 4 years after the operation. At that time she was breathless on moderate exertion, NYHA grade 2b, was orthopnoeic, and had frequent episodes of nocturnal dyspnoea and palpitation.

Abnormal physical signs were confined to the cardiovascular system. The heart rate was 110/min, in atrial fibrillation. There were no signs of fluid retention. The cardiac impulse was unremarkable,

Table *Haemodynamic results at catheterisation*

	Pressures (mmHg)				*Mitral valve diastolic gradient (mmHg)*	*Cardiac output (ml/min)*	*Mitral valve area* (cm^2)
	Pulmonary artery	*Left atrium (mean)* *Direct*	*'Indirect'*	*Left ventricle*			
Case 1	65/32 (42)	30		130/ –28	0	2500	>4
Case 2	60/35 (42)		32	140/10–25	7	2400	1·3
Case 3	35/12 (20)		12	130/ 8–20	3	3600	1·7

Note: The two diastolic left ventricular pressures given are early and end-diastolic figures. The figure in brackets after the pulmonary artery systolic and diastolic pressures is the mean. Mitral valve area refers to the estimate obtained using the formula of Gorlin and Gorlin (1951).

but on auscultation there was accentuation of the pulmonary component of the second heart sound, an opening snap, and grade 2/4 mid-diastolic murmur. The chest *x*-ray film showed slight cardiomegaly, left atrial enlargement, and upper lobe venous engorgement. The electrocardiogram confirmed atrial fibrillation and showed right ventricular hypertrophy.

The echocardiogram showed that the peak diastolic closure rate of the anterior mitral valve was reduced (9 mm/s) and there was forward movement in diastole of the posterior cusp. Peak rate of increase in transverse cavity dimension was reduced to 5 cm/s and outward wall movement continued throughout diastole (Fig. 4).

Cardiac catheterisation data are displayed in the Table. There was a small measured mitral valve gradient of 7 mmHg (mean) and the left atrial and ventricular pressures equalised at end-diastole at 25 mmHg. Left ventricular wall excursion was reduced; the estimated ejection fraction (based on single plane angiogram) was 38 per cent.

Although the measured gradient was slight and there were features to suggest left ventricular disease, it was eventually decided to recommend surgery. At open exploration the mitral valve orifice was estimated to measure 1 cm by 0·5 cm. It was possible to conserve the valve by commissurotomy and separation of the fused chordae tendineae.

In the 3 years since her operation, she has fared well, with breathlessness only on severe exertion. She consented to repeat left heart catheterisation, which was performed 4 months after surgery. At that time, the echocardiographic assessment was that filling was normal—peak rate of wall separation was 14 cm/s. Left ventricular end-diastolic pressure was 10 mmHg and the angiographic ejection fraction had increased to 70 per cent.

Case 3

This man was investigated at the age of 36. He had had rheumatic fever 4 times between the ages of 14 and 25, and, when he was 27, he was treated for 6 months for endocarditis. After this, he remained symptom free until the year that he was investigated, when he developed right hypochondrial pain and rapidly progressing breathlessness on exertion. At the time when he was admitted to the Brompton, he was breathless on mild effort, NYHA grade 3, easily fatigued, and orthopnoeic. He had had haemoptysis and frequent episodes of paroxysmal nocturnal dyspnoea and palpitation.

He was in sinus rhythm; heart rate was 72/min, and blood pressure was 160/90 mmHg. The jugular venous pressure was normal, but the liver was tender. There was no peripheral oedema. The cardiac impulse was unremarkable, but auscultation revealed accentuation of the first heart sound, an opening snap, and grade 2 mid-diastolic murmur at the apex.

The electrocardiogram showed sinus rhythm with left atrial hypertrophy. The chest *x*-ray film showed slight pulmonary vascular congestion. The cardiac silhouette suggested left atrial enlargement.

An echocardiogram showed movement of the mitral valve cusps typical of rheumatic mitral

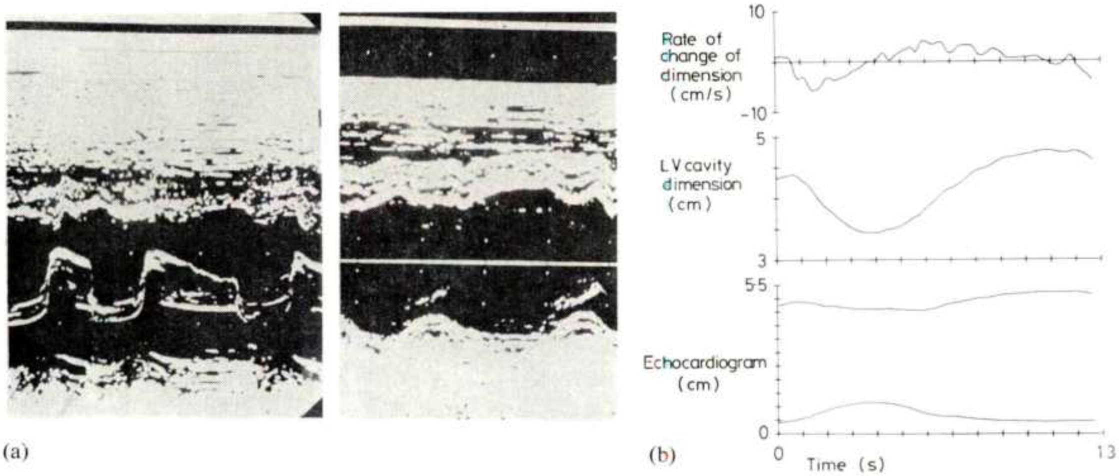

Fig. 4 (a) *Case 2: echocardiograms showing mitral valve echoes on the left, and the left ventricular cavity on the right.* (b) *Case 2: plots of original digitised echocardiogram, the left ventricular cavity dimension, and its rate of change.*

stenosis, and peak diastolic rate of change of transverse dimension was reduced. Increase in dimension at a slow rate proceeded throughout diastole without either a rapid filling phase or an increase at the time of atrial systole. End-diastolic dimension was 5·2 cm.

Cardiac catheterisation was performed because of the suspicion of additional left ventricular disease. The mean mitral valve gradient was 3 mmHg and the left ventricular end-diastolic pressure was raised to 20 mmHg. The left ventricular cineangiogram showed a normal pattern of contraction with ejection fraction 70 per cent.

He was referred for open exploration. The surgeon reported the valve to be severely stenosed with an orifice of less than 1 cm, and the chordae were shortened. Open mitral valvotomy was performed, since when he has been asymptomatic.

Discussion

We report 3 patients who presented with mitral stenosis and breathlessness, in whom the results of haemodynamic investigations could have led us to consider myocardial disease as the cause of their symptoms. They exemplify the more general problem of distinguishing the mechanical effect of rheumatic heart disease from the 'myocardial factor'. Until recently, the two tests most generally considered reliable in this context have been cardiac catheterisation and left ventricular cineangiography, the former to estimate the pressure gradient, flow, and hence valve area, and the latter to examine wall movement. It has been suggested (Harvey *et al.*, 1955; Fleming and Wood, 1959) that characteristic features of patients with predominant myocardial disease are a mild rise in left atrial pressure and a low cardiac output which fails to increase with exercise, but these are unreliable (Carman and Lange, 1961).

Among reports of the value of simultaneous recordings of left ventricular and left atrial pressures are a number of patients like those reported herein who had severe mitral stenosis with small gradients (Hancock, 1959; Dutrey and Drake, 1961; Hugenholtz *et al.*, 1962; Leach *et al.*, 1962), but they received little attention. If such anomalous findings were discussed at all, they were attributed to tech-

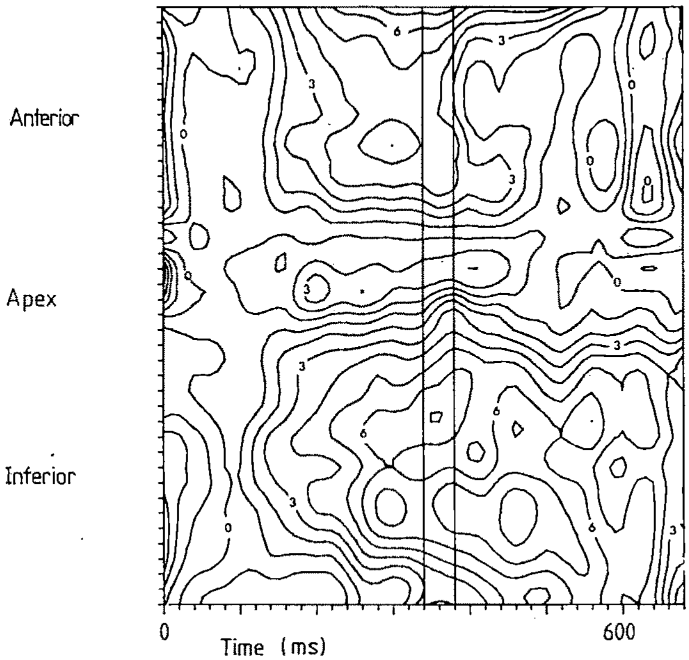

Fig. 5 *Case 2: computer display of endocardial movement in all regions of the angiographic cavity during a single cardiac cycle. Each contour line represents 1 mm movement. The first vertical time marker indicates end-systole and the second mitral valve opening. The diastolic contour lines are spaced widely and evenly, similar to those in systole, indicating that outward movement is slow and persists throughout diastole.*

nical factors until Feigenbaum and co-workers (1966) argued that they indicated 'abnormal ventricular compliance', either as a consequence of rheumatic carditis, or because of the effect on the adjacent myocardium of fibrosis and stiffening of the posterior mitral leaflet and chordae, already described by Grant (1953) in necropsy specimens. Support for the latter hypothesis is provided by observations of regional abnormalities of wall movement in left ventricular cineangiograms (Heller and Carleton, 1970). Thus the unusual findings in the present patients are in keeping with previous observations in suggesting the need to modify the traditional 'bottle-neck' model of the effects of mitral stenosis on the circulation, to reconsider the effects of this condition on left ventricular wall movement, and to review the significance of the left ventricular end-diastolic pressure.

Mitral stenosis affects left ventricular wall movement in two ways. Characteristically slow and protracted filling (Heller and Carleton, 1970) is reflected by the pattern of endocardial movement in all regions and is thus easily demonstrable on the echocardiogram (Gibson and Brown, 1973; St. John Sutton *et al.*, 1977) or by angiography. Fig. 5 shows a display of left ventricular endocardial movement around the whole perimeter of the cavity from the left ventricular cineangiogram of case 2. The pattern of change in endocardial position or cavity dimension, however displayed, is not the normal biphasic curve corresponding to rapid filling followed by diastasis, but instead change is gradual and persists at close to its maximum rate throughout diastole. In addition, regional abnormalities of wall movement may be demonstrated in many patients, usually involving the inferobasal segment adjacent to the mitral valve, and less frequently other regions also (Heller and Carleton, 1970; Curry *et al.*, 1972; Horwitz *et al.*, 1973). Though this second type of abnormality was not pronounced in any of our 3 patients, the fact that focal abnormalities may occur indicates the existence of factors besides merely inflow obstruction governing wall movement during filling.

The high left ventricular diastolic pressure is further evidence that in these patients filling was influenced by factors below mitral valve level. The significance of this finding in relation to myocardial disease is not straightforward (Braunwald and Ross, 1963) and it is not necessarily the case that, as implied by Feigenbaum, the myocardium is inelastic. The normal mechanism of filling is such that the majority of the diastolic increase in cavity size, which occurs during rapid filling, is achieved with minimal increase in wall stress (Fig. 6) (Gibson and Brown, 1974; Rankin *et al.*, 1977), and it is only during the latter part of diastole and over a short range of dimension that the myocardium exhibits linear elastic behaviour. It follows that a rise in the end-diastolic pressure can be the result of more than one kind of abnormality. For example, decreased compliance, resulting from myocardial hypertrophy, can be measured as an increase in slope of the last part of the stress strain relation, and leads to a high value of end-diastolic wall stress. Alternatively the

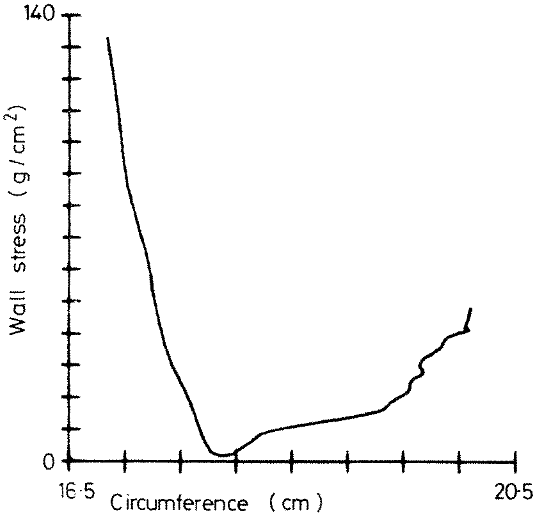

Fig. 6 *Diastolic stress-strain relation in a normal subject estimated from simultaneous recordings of left ventricular pressure and echocardiogram.*

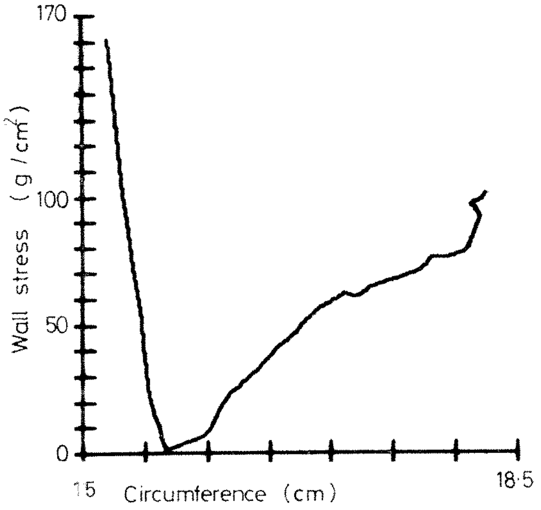

Fig. 7 *Case 2: diastolic stress-strain relation obtained as in Fig. 6. After ventricular relaxation, wall stress increases steeply, even at small cavity size.*

same high value could be associated with normal modulus of elasticity and absence or attenuation of the middle part of the curve. This is exemplified by case 2, in whom the proportional relation between wall stress and strain begins after only a small increase in dimension, so that though the slope is not increased, at the end of diastole wall stress is high (Fig. 7). This is not the effect of reduced compliance, nor is it the result of abnormal viscosity, since viscous forces should be lessened in a situation where filling rate is reduced, and it is therefore difficult to conceive of an explanation in terms of altered material properties of the myocardium. The alternative, which is in keeping with the angiographic evidence, and with the knowledge that surgery effectively relieved symptoms, is that there is an architectural abnormality of the ventricle, the result of rheumatic disease, which affects diastolic function by disruption of a mechanism which normally permits rapid filling.

It seems then that an effect on left ventricular wall mechanics predominated over obstruction at valve level in determining the findings at cardiac catheterisation. The anatomical basis for this is unknown, for the patients are living, but it is to be noted that Grant (1953) described myocardial abnormalities in this condition affecting regions of the left ventricular wall which had been splinted by fibrosis and stiffening of the subvalve apparatus. Regional abnormalities of function may influence the diastolic properties of the whole ventricle in other conditions besides mitral valve disease, for example coronary artery disease, where again a rise in the left ventricular diastolic pressure need not reflect global alteration in myocardial compliance. We conclude that in some patients with significant mitral stenosis haemodynamic data, even when technically above reproach, may be misleading. The critical abnormality for assessing severity appears to be the disturbance of filling, apparent in the pattern of endocardial movement. This is demonstrable by echocardiography in the majority of patients, and if not then it may be shown with a left ventricular cineangiogram. As echocardiographic investigation becomes more prevalent and catheterisation is required less frequently patients such as these may cease to be recognised and will no longer cause diagnostic uncertainty.

We thank Dr R. V. Gibson and Dr M. Honey for permission to report on their patients. Dr Honey performed the cardiac catheterisation in case 1.

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Clinical and haemodynamic evaluation of mounted porcine heterograft in mitral position

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SUMMARY Clinical and haemodynamic assessment has been made of 24 patients with porcine heterograft mitral valve replacements. Twenty patients had a good clinical result and were studied electively and 4 patients had persistent symptoms caused either by poor left ventricular function, aortic paraprosthetic regurgitation, mitral paraprosthetic regurgitation, or impaired left ventricular function with a rather small mitral valve area of 1·4 cm^2. The mean left ventricular end-diastolic pressure was 17·8 ± 1·2 mmHg and the mean mitral valve diastolic gradient was 5·9 ± 1·0 mmHg. The larger prostheses had the smaller gradients. The average mitral valve area was 3·2 cm^2 for 35 mm valves, 2·8 cm^2 for 33 mm valves, 2·1 cm^2 for 31 mm valves, and 2·3 cm^2 for 29 mm valves. Two patients showed significant mitral regurgitation on left ventricular cineangiography but in the remainder the valves were competent.

An apical diastolic murmur was audible in 9 of 24 patients but there was no correlation between the presence of a murmur and the magnitude of the mitral valve gradient or mitral valve area. Nine patients with soft apical systolic murmurs had no evidence of mitral regurgitation but 2 patients with louder murmurs had significant regurgitation.

We conclude that the haemodynamic indices observed with porcine heterograft valves are similar to those observed with other mitral valve prostheses and that though most patients have distinct symptomatic improvement significant haemodynamic abnormalities persist. Apical systolic and diastolic murmurs can be present with normal prosthetic valve function.

Carpentier and Dubost (1972) suggested glutaraldehyde as a method of stabilising porcine aortic valves and Reis and his associates (1971) described the use of a flexible stent on which such valves could be mounted and used as prostheses. These advances were followed by the successful use of mounted porcine heterograft valves in many centres (Brown *et al.*, 1974; Carpentier *et al.*, 1974; Horowitz *et al.*, 1974; Cohn *et al.*, 1975; Johnson *et al.*, 1975; McIntosh *et al.*, 1975; Hannah and Reis, 1976; Sang *et al.*, 1976; Stinson *et al.*, 1977). Their major advantage has been the diminished need for long-term anticoagulation (Cohn *et al.*, 1975; Stinson *et al.*, 1977), while the main disadvantage, as with other tissue valves, has been concern about their long-term durability (Roberts, 1976). As yet few clinical and haemodynamic studies of these valves have been available. This report concerns the appraisal of a group of patients in whom the clinical and haemodynamic function of their implanted mounted porcine heterografts has been assessed. All of the prostheses described in this report were manufactured by Hancock laboratories.

Subjects and methods

Twenty-four patients were studied 4 to 32 months (mean 14 months) after implantation of a mounted porcine heterograft in the mitral position. In 4 patients postoperative haemodynamic assessment was indicated because of continuing symptoms. The other 20 were restudied electively after giving informed consent.

At cardiac catheterisation simultaneous pulmonary capillary wedge pressure and left ventricular pressure were recorded at the same gain with zero level set at mid chest. Left atrial pressure was recorded in case 24. Pulmonary artery wedge pressures were accepted if the pressure contour was distinctly different from, and the phasic and mean pressure were lower than, those recorded

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from the pulmonary artery. The 8 patients in sinus rhythm had a biphasic pulmonary artery wedge pressure trace. Mean mitral valve gradient was obtained by averaging values for 5 cardiac cycles. Mitral valve area was calculated using the Gorlin formula (Gorlin and Gorlin, 1951). Cardiac output was measured by the Fick principle using measured oxygen uptake and arteriovenous oxygen difference. Left ventricular angiography was performed in the right anterior oblique position. The ejection fraction was measured by the area length method of Greene (Greene *et al.*, 1967), and the competence of the mitral valve was assessed. A proportion of patients had preoperative haemodynamic data which have been tabulated with the postoperative results. Four patients had pre-

Table

Case no.	*Age (y)*	*Sex*	*Diagnosis*	*Rhythm*	*HR (beats/min)*	*MPA (mmHg)*	*PAW (mmHg)*	*LVEDP (mmHg)*	*CI (l/min per m²)*	*MVA (cm²)*	*MVG (mmHg)*	*Ring size (mm)*	*EF (%)*	*Other procedure*	*NYHA class*	*Angiography*	
																MR	*AR*
1	57	F	RHD MS MR	AF	82	32	18	18	NA	NA	0	31	53	—	I	0	
2	61	F	RC MR	NSR	75	36	26	24	3·6	3·3	7	33	52	—	I	0	
3	69	M	RHD MS MR	AF	53	32	22	21	2·4	1·7	4	31	63	TA	I	0	
4	43	F	RHD MS	NSR	77	37	30	27	2·9	2·1	10	29	51	—	I	0	
5	51	M	RHD MS	AF	50	40	30	25	1·7	—	0	33	44	—	I	0	
6	54	M	RC MR	AF	70	20	15	16	2·0	3·6	1	35	73	—	I	0	
7	60	F	RHD MS MR	AF	75	27	22	20	2·0	2·1	5	31	73	—	II	2/3	
8	58	M	Cleft MV	AF	51	31	24	23	1·4	2·1	3	33	10	—	II	0	
9	66	F	IHD RPM	AF	78	32	22	15	3·1^{E}	2·6	6	31	52	CABG	I	0	
10	57	M	RHD MS MR	AF	66	27	19	17	3·6	3·1	3	35	74	—	II	0	
11	50	M	RHD AS MPS	AF	77	30	24	20	2·3	1·6	8	29	49	AVR	III	0	2/3.
12	49	F	RHD MS MR	AF	97	36	23	16	2·5^{E}	2·0	8	31	39	—	I	0	
13	36	M	RHD MR AR	AF	59	30	24	15	3·7	2·4	15	31	29	AVR	III	0	0
14	35	M	RHD MS MR	NSR	71	19	9	8	4·1	3·5	5	33	50	—	I	0	
15	39	F	RHD MS	NSR	66	23	15	15	4·0	3·3	6	29	62	—	I	0	
16	34	F	RHD MS MR	NSR	75	23	17	10	5·4	—	0	33	73	—	I	0	
17	55	M	RHD MS	AF	68	22	12	14	2·6	1·8	4	31	59	—	I	0	
18	54	F	RHD MS MR	AF	61	32	23	19	4·1	2·1	10	31	88	—	I	0	
19	66	M	RHD SBE AR MR	NSR	72	37	33	25	3·1	1·3	21	31	61	—	II	0	
20	41	F	RHD MR MS AR	AF	61	15	8	8	2·5	2·2	3	33	63	—	II	0	
21	43	M	RHD MR	AF	69	20	15	14	3·7	3·1	3	35	58	—	I	0	
22	51	F	RHD MS	NSR	98	35	20	13	3·2	1·7	10	31	53	—	II	0	
23	59	M	IHD MR	NSR	120	42	36	30	2·3	3·0	1	35	10	CABG	III	0	
24	36	F	RHD MPR	AF	115	40	35	15	5·0	3·0	8	31	NA	—	III	2/3	
Mean	51				74·4	29·9	21·7	17·8	3·1	2·46	5·9		53·9				
±SEM	2·1				3·6	1·5	1·5	1·2	0·21	0·15	1·0		3·9				

AF, atrial fibrillation; AR, aortic regurgitation; AS, aortic stenosis; AVR, aortic valve replacement; CABG, coronary artery bypass graft; CI, cardiac index; E, estimated; EF, ejection fraction; HR, heart rate; IHD, ischaemic heart disease; LVEDP, left ventricular end-diastolic pressure; MPA, main pulmonary artery mean pressure; MPR, mitral prosthetic regurgitation; MPS, mitral prosthetic stenosis; MR, mitral regurgitation; MS, mitral stenosis; MV, mitral valve; MVA, mitral valve area; MVG, mitral valve gradient; NA, not available; NSR, normal sinus rhythm; PAW, pulmonary artery wedge mean pressure; RC, ruptured chordae; RHD, rheumatic heart disease; RPM, ruptured papillary muscle; SBE, subacute bacterial endocarditis; SEM, standard error of mean; TA, tricuspid annuloplasty.

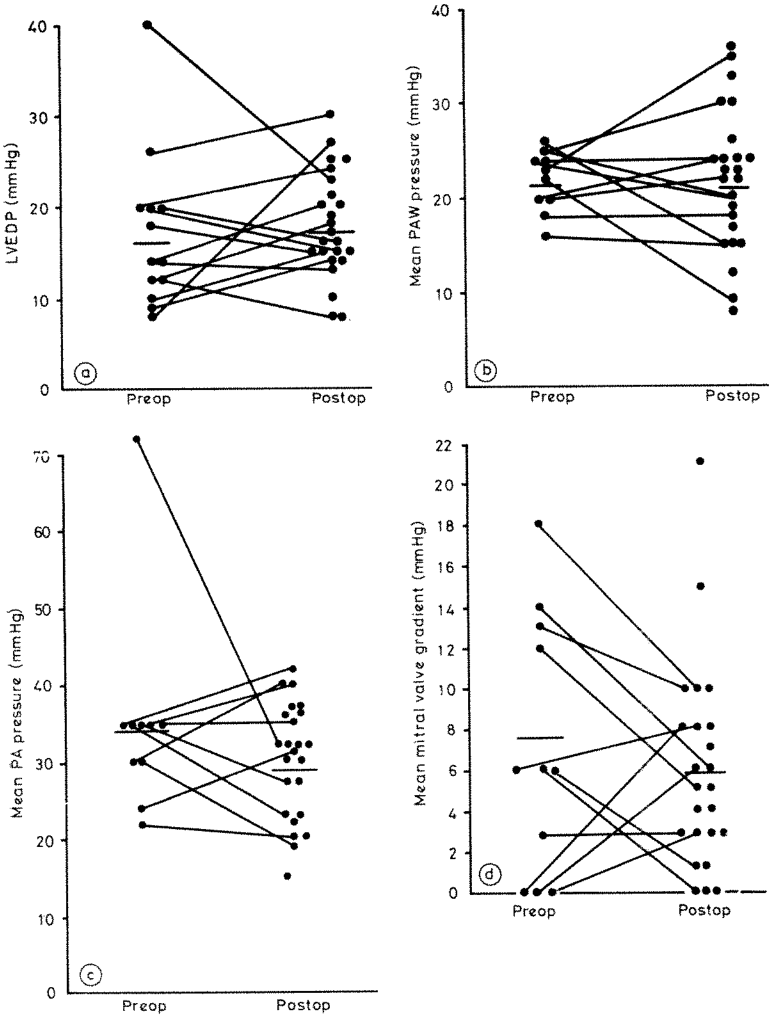

Fig. 1a-1d *Preoperative and postoperative haemodynamic data of mounted porcine heterografts in the mitral position.*

operative coronary angiography which was normal in 2.

Postoperative results

HAEMODYNAMICS

Individual values are shown in the Table and Fig. 1 and standard errors of the mean are given in the text.

The mean left ventricular end-diastolic pressure (Fig. 1a) was 17·8 ± 1·2 mmHg (range 8 to 30 mmHg) compared with an almost identical preoperative mean value of 17·2 ± 2·4 mmHg (range 8 to 40 mmHg) in the 13 patients in whom these data are available. Seven patients showed a rise in left ventricular end-diastolic pressure and in 7 the postoperative values fell. Mean pulmonary artery wedge pressures postoperatively (Fig. 1b) averaged 21·7 ± 1·5 mmHg (range 9 to 36 mmHg) which is almost identical to the preoperative average of 21·8 ± 1·0 mmHg (range 16 to 26 mmHg). The average mean pulmonary artery pressure postoperatively (Fig. 1c) was 29·9 ± 1·5 mmHg (range 15 to 42 mmHg) while the average preoperative mean pulmonary artery pressure was 31·2 ± 1·7 mmHg (range 22 to 72 mmHg). The mean mitral diastolic gradient postoperatively averaged 5·9 mmHg (range 0 to 21 mmHg) (Fig. 1d). The average gradient for the 35 mm stent mounted valve was 2·0 mmHg (range 1 to 3 mmHg), for the 33 mm stent was 3·0 mmHg (range 0 to 7 mmHg), for the 31 mm stent was

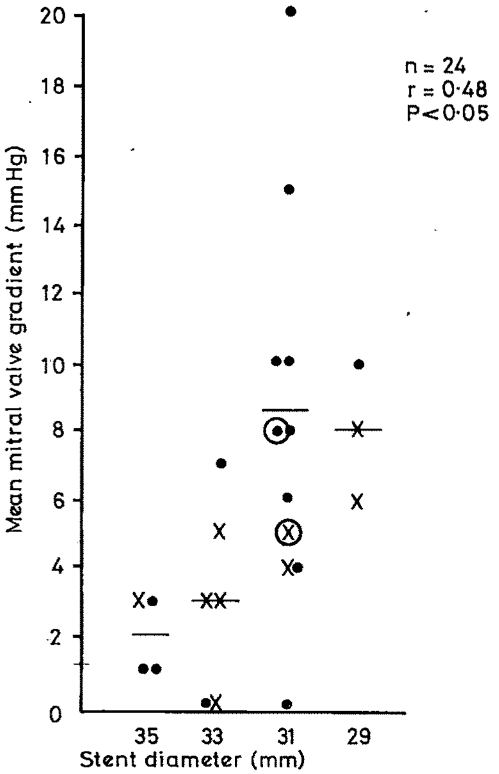

Fig. 2 *Mitral valve gradient related to stent diameter. X, apical mid-diastolic murmur; O, apical pansystolic murmur.*

8·3 mmHg (range 0 to 21 mmHg), and for the 29 mm stent was 8·0 mmHg (range 6 to 10 mmHg). The relation between mitral valve gradient and stent diameter was statistically significant ($r = 0{\cdot}69$, $P < 0{\cdot}05$) as shown in Fig. 2.

Two patients (cases 9 and 13) were unable to perform expired air collection and an estimated oxygen uptake was used to calculate cardiac output (Robertson and Reid, 1952) and to derive mitral valve area. The cardiac index ranged from 1·4 to 5·4 l/min per m^2 with an average of 3·1 ± 0·21 l/min per m^2. The average mitral valve area for 21 patients in whom it could be calculated postoperatively was 2·5 cm^2 (range 1·3 to 3·6 cm^2). The average area for the 35 mm diameter stent valves was 3·5 cm^2 (range 3·0 to 3·6 cm^2), that for the 33 mm stents was 2·5 cm^2 (range 1·1 to 3·5 cm^2), that for the 31 mm stent valves was 2·0 cm^2 (range 1·3 to 3·0 cm^2), while that for the 29 mm stent valves was 2·2 cm^2 (range 1·6 to 3·0 cm^2). Discounting the patients in whom the area could not be calculated (3 patients) the valve area correlated significantly with the stent diameter ($r = 0{\cdot}56$, $P < 0{\cdot}01$).

The ejection fraction averaged 53·9 ± 3·9 per cent (range 10 to 88%). Left ventricular angiography showed important mitral regurgitation in 2 patients but the prosthesis was competent in the remaining 22 patients. Aortography showed important aortic regurgitation in 2 other patients.

Clinical results

Functional improvement from preoperative class III or IV to functional class I or II was noted in 20 of the 24 patients studied (Fig. 3). Of the 4 patients with a poor clinical result, 1 was found to have important mitral paraprosthetic regurgitation (the mean mitral valve gradient was 8 mmHg) and another had severe aortic paraprosthetic regurgitation (mean mitral valve gradient 8 mmHg). A third patient had a mean mitral diastolic gradient of 15 mmHg (valve area 2·4 cm^2) combined with an ejection fraction of 29 per cent. The fourth patient had severe coronary artery disease and an ejection fraction of 10 per cent with a satisfactory prosthesis.

Clinical examination revealed a grade 1 to 2 out of 6 apical mid-systolic murmur in 9 patients, none of whom had angiographic evidence of mitral regurgitation. Two patients with important mitral paraprosthetic regurgitation had grade 3 out of 6 pansystolic murmurs.

Diastolic murmurs were audible at the apex in 9 of the 24 patients. Seven of the murmurs were grade 1 or 2 out of 6, 2 were grade 3 out of 6. There was no correlation between the stent diameter of the mitral valve implanted or the mitral valve area and the presence of a murmur, nor was there

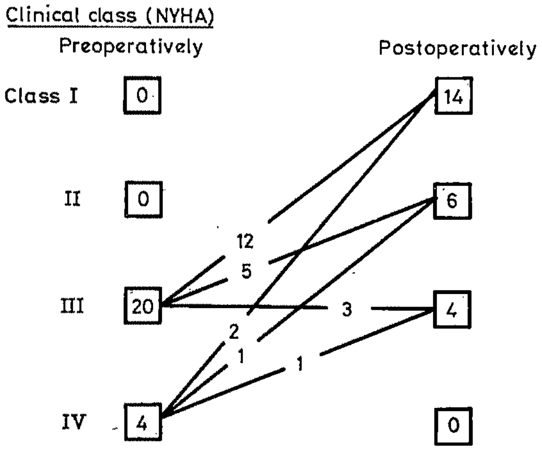

Fig. 3 *Clinical class (NYHA) pre- and postoperatively.*

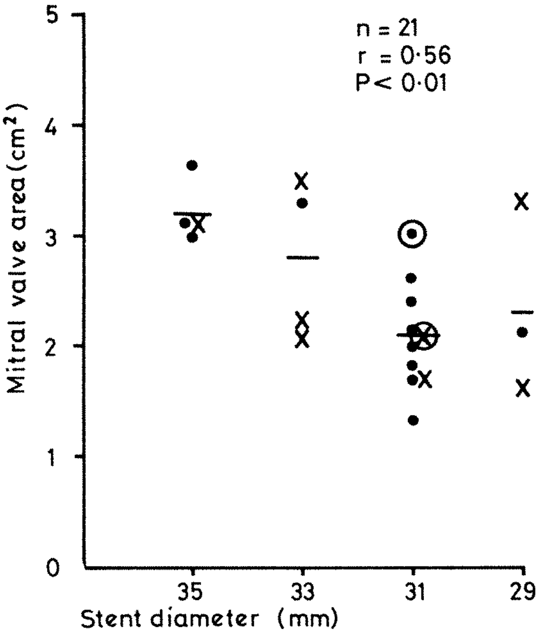

Fig. 4 *Mitral valve area related to stent diameter. X, apical mid-diastolic murmur; O, apical pansystolic murmur.*

any correlation between the presence of a murmur and the size or indeed the presence of a mitral diastolic gradient (Fig. 2 and 4).

Discussion

The majority of patients undergoing mitral valve replacement with a mounted porcine heterograft have a good clinical result (Sang *et al.*, 1976; Stinson *et al.*, 1977). This is also true of other widely used mitral valve prostheses (Winter *et al.*, 1972; Böök, 1974; Brown *et al.*, 1974). The main advantage of the heterograft valve has been the relatively low incidence of thromboembolic complications (Wallace, 1975; Roberts, 1976; Stinson *et al.*, 1977). Our practice has been to anticoagulate our patients for 6 weeks postoperatively and then to stop anticoagulants unless a massive left atrium or atrial thrombus has been found at operation. In this series we have noted no embolic phenomena though we have encountered several major emboli in our total heterograft experience.

The haemodynamic findings in this series are similar to those found by other investigators (Horowitz *et al.*, 1974; Johnson *et al.*, 1975; McIntosh *et al.*, 1975; Hannah and Reis, 1976). Hannah and Reis (1976) found average gradients of 5·2 mmHg, 2·3 mmHg, 2·5 mmHg, and 2·7 mmHg across the 29 mm, 31 mm, 33 mm, and 35 mm stent diameter prostheses, respectively. Johnson and his colleagues (1975) found an average gradient of 5·5 mmHg in the 14 patients they studied while Brown *et al.* (1974) and later McIntosh *et al.* (1975) of the Bethesda group found gradients of up to 15 mmHg, but emphasised that many patients had no gradients. No report of a gradient as high as 21 mmHg found in one of our patients has been made previously. The resting cardiac output was 6·8 l/min and the mitral valve area 1·3 cm^2. This is similar to other patients and the large gradient presumably reflects the high resting cardiac output rather than prosthetic valve dysfunction. Postoperatively this patient had a good clinical result, improving from functional class IV to class II and therefore no further intervention has been contemplated. With this one exception the atrioventricular gradients found with the porcine heterografts are similar to those found across the other commonly used prostheses (Winter *et al.*, 1972; Böök, 1974; Brown *et al.*, 1974; Angell *et al.*, 1977; Ionescu *et al.*, 1977).

Many of our patients had abnormally high left ventricular end-diastolic pressure postoperatively, and reduced ejection fractions. These indices of left ventricular dysfunction did not correlate significantly with the total cardiopulmonary bypass time or with the aortic cross clamp time. Deterioration in left ventricular function after mitral valve replacement has been well documented previously (Hultgren *et al.*, 1968; Gold, 1974; Maloney *et al.*, 1975) but is not fully understood though it may be related to the bypass technique. In this series myocardial preservation with local hypothermia using ice-cold saline was the technique employed. It is striking that in spite of the frequency of significant haemodynamic abnormalities postoperatively, both in terms of left ventricular and valve function, the majority of patients have such obvious symptomatic improvement. This discrepancy between clinical and haemodynamic results is not an infrequent finding after mitral valve surgery, and an abnormality of left ventricular compliance has been suggested as an explanation for the increased left ventricular end-diastolic pressures sometimes encountered (Feigenbaum *et al.*, 1968). Recently Sutton *et al.* (1977) have mentioned several patients with small or absent mitral valve gradients in whom symptoms were relieved by mitral valve surgery. They postulate that removal of the subvalve apparatus is responsible for the improvement and this may be a factor in our cases also.

The presence of systolic murmurs in patients with normally functioning mitral porcine heterografts and no other valvular disease was noted by Horowitz and his colleagues (1974) in 11 of 14 patients. One patient had a mid-diastolic murmur and he had a pannus of tissue interfering with the function of an otherwise normal heterograft, effectively causing mitral prosthetic obstruction. Nine of our patients had systolic murmurs similar to those described by Horowitz *et al.*, with no evidence of mitral regurgitation. In addition, we found mitral diastolic murmurs in 9 of the 24 patients. These murmurs gave no guide to the severity or presence of a transvalvular gradient. In 2 of the patients it is possible that the diastolic murmur was caused by increased flow associated with concomitant mitral regurgitation. Another patient with a mid-diastolic murmur had mild aortic regurgitation and this may have been an example of the Austin Flint phenomenon, which can occur with mitral prostheses (Epstein and Coulshed, 1975; Schaefer *et al.*, 1975). In the other 6 patients with apical mid-diastolic murmurs, however, no such explanation is available and we conclude that apical systolic and diastolic murmurs may be associated with normal prosthetic valve function.

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Measuring the effect of a mobile coronary care unit upon the community

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SUMMARY A mobile coronary care unit working within a geographically defined area retrieved 20 per cent of the estimated number of cases with myocardial infarction. These cases were similar to the population at risk in terms of age, sex, and previous history of ischaemic heart disease.

Patients retrieved by the mobile unit had a lower overall case fatality ratio. This discrepancy was greater than could be explained by resuscitation or preventive treatment by the mobile unit teams. Reasons for this difference in mortality were explored.

The benefits of the mobile coronary care unit were obvious in terms of the existing service but small in terms of the community. Any judgment on the effectiveness of a mobile unit must use both approaches to get a balanced view.

Mobile coronary care units have been set up in many countries (Pantridge *et al.*, 1975). Attitudes towards the founding of new units have varied. The British have been slow to develop them (Dewar, 1975), whereas in the United States the trend has been towards complex systems capable of reaching patients within minutes (Cobb *et al.*, 1975; Nagel *et al.*, 1975).

Mobile coronary care units are a response to a problem: the large number of deaths from ischaemic heart disease in the community before medical aid can be obtained. Their effectiveness depends entirely upon their ability in meeting this problem. However most research work into the use of mobile coronary care units has concentrated on patients seen in and treated by the units, ignoring the community at large from which these patients were drawn. The present study was set up in order to measure the impact of a mobile coronary care unit upon the population with ischaemic heart disease in a defined area.

Patients

Two hundred and twenty-seven patients, initially suspected of having had a myocardial infarction, were seen by the mobile coronary care unit in a period of 14 months. One hundred and fifty-eight were proved to have had a myocardial infarction and a further 10 had a history strongly suggestive of infarction but died before a definitive diagnosis could be made. This 168 comprised the study group; 117 were men, 51 were women. Their mean age was 57·5 years, with an upper limit of 69 years.

The patients in the study were restricted to those retrieved from a defined area of 12 electoral wards in the south of Edinburgh, the traditional catchment area for the Royal Infirmary, at which the mobile unit was based. Two hundred and six general practitioners whose practices were wholly or partially in this area were contacted and informed that any patient suspected of having had a myocardial infarction living within these wards would be eligible for treatment by the mobile unit. A proviso was added that any patient from outside the area whom the general practitioner considered required urgent treatment by the mobile coronary care unit would be attended. The latter patients were not included in the present study.

No specific interventions were made regarding treatment of the patients other than those indicated by the therapeutic schedule for the hospital coronary care unit (Lawrie *et al.*, 1967). This most often involved giving analgesics; morphine 10 mg and cyclizine 50 mg usually given slowly intravenously until pain was substantially relieved. Atropine was given for sinus bradycardia if the patient's blood pressure fell below 90 mmHg or

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ectopic beats were seen. The only other drug frequently given was lignocaine for close-coupled (R on T) ectopic beats or ventricular tachycardia.

RETRIEVAL OF PATIENTS

Patients were usually referred to the unit by their general practitioners. If a patient telephoned his or her general practitioner with a history suggestive of ischaemic heart disease the doctor was encouraged to call the mobile coronary care unit directly before seeing the patient. If the patient had had over 20 minutes of chest pain or sudden breathlessness or syncope, he or she was admitted to the hospital coronary care unit in the mobile unit. No patient refused admission if it was advised.

Staffing of the unit was carried out by 7 post-registration doctors with an interest in ischaemic heart disease. They also covered the hospital coronary care unit for the insertion of emergency pacing catheters.

Results

The population, from which the study group was drawn, was defined as those people living in an area to the south of the city of Edinburgh enclosed by 12 voting wards. The area measured 10 miles by 5 and contained 249700 people—approximately 55 per cent of the population of the city.

The mobile coronary care unit had an upper imposed age limit of 69 years because of the policy of the hospital coronary care unit at which it was based; no patients were retrieved under 20 years of age. An estimate was made of the number of people in this population who had had an attack of ischaemic heart disease. This was made using data from the Edinburgh community study (Armstrong *et al.*, 1972) which was performed 3 years before. There was no pronounced change in the mortality from ischaemic heart disease over that period in Edinburgh, being 4·54 per 1000 for people between 35 and 75 years of age during the community study and 4·58 per 1000 in the year of the present study. It was, therefore, inferred that the morbidity from ischaemic heart disease during that period had not varied greatly.

Episode rates of ischaemic heart disease were taken from the community study and multiplied by the population at risk to give the expected number of attacks.

During the community study it was discovered that some of the most important data on patients with ischaemic heart disease were hidden in 2 ways. One group, the unattended deaths, was obtained by examining the death certificates of patients; the other group had insufficient data for a definitive diagnosis but some subjective evidence that the patients had sustained a myocardial infarction. As both groups of patients had died very soon after the onset of their symptoms, they were included in the comparison with the service which was aimed at the retrieval of such early deaths. The estimated numbers in the present study include both of these groups.

Eight hundred and thirty-six episodes of myocardial infarction were estimated to have occurred in the catchment area of the mobile coronary care unit during the period of the study. In fact the unit attended 168 (21%) patients with myocardial infarction or sudden death.

The small proportion of cases actually carried by the mobile unit made it essential to test, as far as possible, the degree to which the study group was typical of the population in the study area with myocardial infarction. In particular any factors liable to affect the case fatality ratios of the two groups required to be examined.

Several categories of these data were examined: demographic, social, previous history, and factors with special relevance to the mobile unit, the time, and place of the attack.

DEMOGRAPHIC DATA

Table 1 shows the age and sex breakdown of the patients with myocardial infarction seen in the mobile coronary care unit compared with those attacks of myocardial infarction estimated to have occurred over the same period in the community. Despite the low proportion of patients seen by the mobile unit, their age and sex categories were very similar to those expected from the community data. Age and sex are known to be related to the outcome of an attack. Armstrong *et al.* (1972) have shown increasing fatality ratios with age and a slightly higher ratio in women than men.

The relation between mortality and social factors is more complex. Standardised mortality ratios are lower in Scotland for the higher groups in the Registrar General's social class classification, but this may reflect a variation in the attack rate. A paper by Colling *et al.* (1976) was one of the few to describe community morbidity in terms of social class and found a high proportion of social class I and II. They did not relate these findings to mortality. However, social factors normally play such an all-pervading part in the prevalence of disease that it was thought to be important to describe the study group in this way. In this study group social classes I and II had a lower case fatality ratio (15%) than social classes IV and V (29%) though these differences were not significant at a 5 per cent level.

Table 2 shows the study group by social class

Table 1 *Observed and expected episodes of myocardial infarction in the population at risk*

	Men				*Women*				*All*
	20–	*50–*	*60–69*	*Total*	*20–*	*50–*	*60–69*	*Total*	
Population (1000s)	45·3	13·2	11·9	70·4	47·9	16·2	16·2	80·3	150·7
Observed (in MCCU)	19	45	52	116	5	15	31	51	167*
Expected (from Community study)	97·1	205·1	288·9	591·1	16·7	60·9	142·1	219·7	810·8
Proportion observed (%)	19·6	21·9	18·0	19·6	29·9	24·6	21·8	23·2	20·6

*Age not known in 1 male patient.

Table 2 *Comparison of social class groupings of study group and other groups with ischaemic heart disease*

	Social class (%)				
	I	*II*	*III*	*IV*	*V*
Study group	4·3	31·2	46·4	15·9	2·2
Study population	7·9	12·1	57·4	13·5	9·1
Cay *et al.* (1972) (hospital)	4·4	20·7	31·0	25·1	18·7
Colling *et al.* (1976)	14·7	17·4	59·4	13·7	4·9
Edinburgh mortality	7·7	11·5	60·8	13·0	10·2

Goodness of fit test: study group vs study population. χ^2_4 = 65·2, P < 0·0001, that is highly significant difference in composition by social class.

Table 3 *Comparison of previous cardiac disease between study group and other community data (%)*

	Previous infarction	*Previous angina*	*Increased angina (1/12)*
Study group	32	69	32
Edinburgh community study (Armstrong *et al.*, 1972)	30	—	—
Tunstall-Pedoe *et al.* (1975)	35	40	—
WHO Registers (WHO, 1976)	30	50	36

Goodness of fit: previous angina for study group vs WHO registers: χ^2_1 = 12·1, P < 0·0005, that is highly significant difference in attack rate.

compared with the general population in the study area, hospital patients in Edinburgh with ischaemic heart disease (Cay *et al.*, 1972), the Teesside community study (Colling *et al.*, 1976), and deaths from myocardial infarction in Edinburgh. The study group appears to have an excess of people in social class II and a low proportion of social class V. This together with the relatively low case fatality in the higher social classes suggest that general practitioners were calling the mobile unit selectively for people in social class II.

PREVIOUS HISTORY OF HEART DISEASE

A previous history of heart disease has been shown to have a relation with prognosis in several hospital-based indices (Peel *et al.*, 1962; Norris *et al.*, 1969), and in civil servants in the community (Rose *et al.*, 1977). Table 3 shows the proportion of patients with a previous history of heart disease in 2 community studies (Armstrong *et al.*, 1972; Tunstall-Pedoe *et al.*, 1975) and the overall figure for the WHO community registers (WHO, 1976).

The study group differed from the community figures in its higher proportion of patients with long-standing angina. This would be expected to have less effect on prognosis than angina of recent onset. The Table shows that, in the latter case, the study group had a proportion of patients affected similar to that seen in the WHO study.

SPACE AND TIME

By the nature of the service it might be expected that patients at a distance from the base station would be less likely to be retrieved. Some general practitioners might have considered that the time taken for the mobile unit to arrive would undermine its usefulness to patients at a distance.

The cases retrieved were examined by their electoral ward of residence and the proportion of observed cases compared with the numbers expected. The expected cases were calculated from the age and sex structure of each ward using the episode rates from the community study. There was no pattern of under- or over-usage of the mobile unit in relation to the distance from the Royal Infirmary (mean 20·1%; standard deviation for 12 wards, 3·1%).

The general practitioners who called the unit were biased against using it at night. The World Health Organisation myocardial infarction community registers showed that 53 per cent of all attacks of myocardial infarction began in daytime (0600-1800); Tunstall-Pedoe *et al.* (1975) also showed 52 per cent starting within that time. In the present study group 70 per cent of patients had the onset of their attacks between these hours. There were no differences of this type for the day of the week or the month of the year.

These variations in time and space were not use-

Table 4 *Outcome—cardiac arrests and non arrests*

		Men			*Women*		*Total 20-69*
		20-	*50-*	*60-69*	*20-*	*60-69*	
No cardiac arrest within 4 weeks		19	29	33	16	21	118
Survivors of cardiac arrest within 4 weeks	Arrested at home	0	3	3	1	3	10
	Arrested in MCCU	0	0	0	0	0	0
	Arrested in hospital	0	3	3	1	1	8
	Total	0	6	6	2	4	18
Died of cardiac arrest within 4 weeks	Arrested at home	0	4	4	2	1	11
	Arrested in MCCU	0	0	0	0	0	0
	Arrested in hospital	0	6	10	0	5	21
	Total	0	10	14	2	6	32
Overall total		19	45	53	20	31	168

Three patients arrested at home and again in hospital: 2 survived 4 weeks, 1 died.
Counted in first place of attack only.

ful for assessing the relative severity of the study group against the community, for the relation between those variables and severity of disease is unknown. The time of onset made little difference to the outcome, for the patients seen by the mobile unit had a mortality of 19 per cent in the day-time compared with 20 per cent for those whose symptoms began at night. These factors do however highlight the unexpected ways in which such a system may cause bias and the degree to which this can cause differences between patients retrieved and the community at large.

OUTCOME

Table 4 shows the patients in the study group classified by whether or not they suffered a cardiac arrest. These are also categorised by the place of their first arrest and by age/sex groups. Ten of the patients who arrested at their place of attack died there and a definitive diagnosis of myocardial infarction could not be made on these patients. One other survived the initial arrest at the place of the attack but died later in hospital.

There was an increased proportion of cardiac arrests among the older age groups. The greatest percentage was seen in men aged 60 to 69, with 20/53 (38%) suffering an arrest at some time, of whom 14 died. Overall, 32/168 (19%) of patients died within 4 weeks of the onset of their symptoms; the majority (30) at the place of the original arrest.

Resuscitation was successfully carried out in 18 patients. In 10 this was initiated at the place of onset of the attack and was carried out by the mobile unit team. A further 8 patients were successfully resuscitated after a first arrest in hospital. No cardiac arrests occurred in the mobile coronary care unit while it was transporting patients to hospital, nor did any occur as the patient was being moved into the mobile unit.

The incidence of cardiac arrests is closely related to the time after the onset of a patient's symptoms. Table 5 shows these data for the study group. Thirteen/47 (29%) of patients seen initially within an hour of the onset of their symptoms had a cardiac arrest when they were first seen at home by the mobile unit team. This compared with 5/76 (7%) for patients first seen between 1 and 4 hours and 2/42 (5%) after 4 hours.

OUTCOME—COMPARISON BETWEEN STUDY GROUP AND COMMUNITY

Thirty-two of 168 patients (19%) seen by the mobile coronary care unit died within 4 weeks of the onset of their symptoms compared with 42 per cent expected from the community data. This difference was not the result of resuscitation by the mobile unit for if the successfully resuscitated cases had died there would have been 43 deaths (25%), still significantly less than the proportion expected in the community.

The major determinant of mortality after myocardial infarction is the time after the onset of the acute event. It was likely to be a major source of bias when comparing a retrospective community survey with a group entering the study at different times after medical aid had been summoned.

Table 6 illustrates this. The first section (A) shows data from the community survey, with the deaths in time intervals after the onset of the patient's symptoms. The next (B) shows data for the patients seen in the mobile coronary care unit. The third (C) shows the same data with all cardiac arrests in the mobile unit, including those successfully resuscitated, counted as deaths. This group was included to test the effect of resuscitation by the mobile unit. See appendix for a more detailed explanation of Table 6.

It is an inevitable limitation of this study that the small numbers at risk make the figures for patients seen in the first hour particularly susceptible to bias.

Table 5 *Outcome—time patients initially seen after onset of symptoms related to patients with and without cardiac arrest*

Place of event	*At home*	*Hospital CCU*	*Hospital ward*	*Returned home*
Time after onset 0–1 hours				
Number of patients	47 →	38 →	33 →	31
Cardiac arrests	13	10	2	
Died	9	5	2	
Resuscitated	4	5	0	
Time after onset 1–4 hours				
Number of patients	76 →	75 →	66 →	63
Cardiac arrests	5	12	3	
Died	1	9	3	
Resuscitated	4	3	0	
Time after onset over 4 hours				
Number of patients	42 →	42 →	41 →	39
Cardiac arrests	2	1	2	
Died	0	1	2	
Resuscitated	2	0	0	

Data of time after onset not available for 3 patients.

This, together with the large number of cardiac arrests within this time interval resulted in extremely high case fatality ratios compared with the number expected. Two factors probably played a part in this; firstly the mobile unit was called more quickly to patients who had already arrested than to those who had not. As arrests were more common within the first hour the mobile unit saw a disproportionate number of them at that time. Secondly, the patients at risk entered the study for an average of only 17·4 minutes in the first hour. Some patients had arrested before they officially entered the study, when the mobile unit arrived, artificially increasing the observed number of arrests compared with the average number of patients at risk. This problem could be avoided by counting only cardiac arrests which occurred after the mobile unit arrived. In either case no proper comparison can be made for this group between the mobile unit patients and the community other than to say that there were many cardiac arrests within the first time interval in all groups.

For the remaining time (1 hour to 4 weeks) 23 patients died in the mobile unit compared with 40·9 expected. This difference was highly statistically significant ($P = 0{\cdot}005$). If resuscitation by the mobile unit was ignored the number of deaths was still less than expected, with 29 observed against 38·1 expected, but the difference was not statistically significant ($P = 0{\cdot}13$).

Discussion

This was an observational study of the use of a mobile coronary care unit within a defined area. These data were compared with morbidity and mortality figures from the community obtained some years earlier. In this way it was hoped to put the work of the mobile unit into a community context.

The unit team attended 20 per cent of the estimated number of cases in the community. This small proportion reflected several factors.

The Edinburgh Community Study showed that general practitioners in Edinburgh chose initially to treat 31 per cent of all episodes of ischaemic heart disease at home. An unknown proportion of patients came directly to hospital by their own transport and in up to 4 per cent the attack will have started in hospital (Tunstall-Pedoe *et al.*, 1975). The mobile unit was a new service at the start of this study and such services take some time to become accepted. The Belfast workers (Pantridge *et al.*, 1975) retrieved increasing numbers of patients each year over the first 4 years of the service.

The patients seen by the mobile unit were similar in age and sex, previous history of heart disease, and place of the acute attack, to the population with ischaemic heart disease. There were differences in social class structure and the time of day of the attack. This suggests that general practitioners were using the unit selectively for the higher social class patients and those seen in the day-time. General practitioners were expected to stay with a patient if they called the mobile unit; thus calling the unit was more time consuming than calling a city ambulance. This may have caused some of the bias against the unit at night.

The factors measured in order to compare the structure of the two groups were obviously not good able 6 *Comparison between study group and community at various time intervals after onset of symptoms (see Appendix)*

ime interval ours after onset)	*Community data A*			*Study group B*					*Study group C*				
	Alive at beginning	*Died*	*Proportion who died*	*Seen at beginning*	*Entered study*	*Average no. at risk*	*Died*	**Expected no. of deaths*	*Seen at beginning*	*Entered study*	*Average no. at risk*	*Died + MCCU arrests*	**Expected no. of deaths*
- 1	1010	192	0·190	0	47	13·6	9	2·6	0	47	13·6	13	2·6
- 2	818	21	0·025	38	43	59·5	0	1·5	34	43	55·5	3	1·4
- 4	797	26	0·033	81	33	97·5	2	3·2	74	33	90·5	3	3·0
- 6	771	18	0·023	112	17	120·5	1	2·8	104	17	112·5	3	2·6
-12	753	29	0·039	128	14	135·0	1	5·2	118	14	125·0	1	4·8
-24	724	24	0·03	141	8	145·0	4	4·8	131	8	135·0	4	4·5
-48	700	28	0·04	145	3	146·5	8	5·9	135	3	136·5	8	5·5
- 4 weeks	672	84	0·125	140	0	140·0	7	17·5	130	0	130·0	7	16·3
otal							23	40·9				29	38·1

Expected no. of deaths = proportion who died in the community × average no. at risk.
ata of time after onset not available for 3 patients.

predictors of deaths in this group of patients. This may have been because these patients were seen soon after the onset of their symptoms when a high proportion of the deaths resulted from sudden arrhythmias. Kannel *et al.* (1975) have shown that prediction of these early deaths was notoriously difficult using clinical and demographic data.

Comparison of the outcome between the study group and the community was complicated by the different nature of the two sets of data. Unlike the retrospective community data the mobile unit patients were not all present at the beginning of the study, but were admitted throughout, subtly altering the characteristics of the group with time.

The difficulties of this comparison were greatest for the first hour group where the largest number of deaths and the greatest acceleration of admissions occurred. These fluctuations proved too much for the accurate comparison of the fatality ratios. A partial answer would be to break down the initial time interval into small segments and to count only arrests occurring after the arrival of the mobile unit, but these data were not available from the community study.

The mobile unit patients had a similar fatality ratio to the population at risk between 1 hour and 48 hours, if the effect of resuscitation by the mobile unit was discounted (Table 6C), suggesting that the groups were comparable during that time. If this was the case only resuscitation had any effect upon the community mortality—prophylactic measures, for example antiarrhythmic therapy in the mobile unit, did not significantly reduce the mortality during the time interval to below that seen in the community. After 48 hours there was a reduced number of observed deaths compared with the number expected. The reason for this is not fully understood but it was unlikely to be an effect of the mobile unit at the time.

A recent randomised trial of a mobile coronary care unit (Hampton and Nicholas, 1978) failed to show an advantage of a mobile coronary care unit over a routine ambulance for collecting patients with heart attacks; but only 1 of the 82 patients who arrested in the community survived hospital stay. This is a much lower proportion than has been seen in other studies including the present one (Adgey and Pantridge, 1977; Cobb *et al.*, 1975; Mackintosh *et al.*, 1978), and suggests that they have been unlucky with their patient selection.

One previous study (Crampton *et al.*, 1975) has attempted to relate the effects of a mobile unit to community mortality. They claimed an association between a falling death rate from myocardial infarction and the inception of a mobile unit. However, there was no good evidence that the changes were cause and effect, particularly as the mortality rate from ischaemic heart disease was falling rapidly over the years before the introduction of the unit in the community studied.

The relation between a service effect and the community it serves is complex. Thus the mobile unit in this study resuscitated 6 per cent of its patients with myocardial infarction when still in the community compared with 7 per cent in the hospital unit if the units had no adverse effect. However, the mobile unit saw only 20 per cent of the estimated number of people with myocardial infarction in the community giving an overall reduction in the mortality rate of, at most, 1·2 per cent over 4 weeks. The effect upon the Registrar General's annual mortality figures will be well within the random changes expected from environmental factors from year to year. Nor would such differences be detected by a community study of manageable size.

The proportion of patients retrieved could have been increased by administrative changes: taking calls directly from the public and education in resuscitation methods have had an effect elsewhere (Black and Brown, 1973). Alternatively the resources used by the service can be increased. This has been attempted in several places, notably Seattle where 3 mobile coronary care units and several back-up units were combined with a massive public education programme in resuscitation.

Using these resources the Seattle group attended 55·3 persons per 100000 population per annum with 9·6 per 100000 saved each year. The equivalent in this study was 5·4 persons seen and 2·9 per 100000 saved. Thus the Seattle group was able to save 3 times the number of patients compared with the Edinburgh unit.

Within the realms of the possible the mobile coronary care unit is the only available method of treating a cardiac arrest in the community. Whether a mobile unit is worth having in a community is a value judgment which must be based upon the balance of its success with the patients it retrieves, its failure to reach many requiring help, and the resources available. This paper has emphasised that this is not a simple exercise.

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Appendix

Section A of Table 6 shows data from the Edinburgh community study (Armstrong *et al.*, 1972) with the proportion of patients who died within each time interval. Sections B and C are similar to each other. In the first column, 'seen at beginning', is entered the number of patients in the study group seen alive at the beginning of the time interval. The second column 'entered study' shows the number of patients with myocardial infarction *first* seen by the mobile unit within that time interval. The third column 'average no. at risk' relates to the average number of patients at risk of dying during the time interval.

As patients are entering the study, that is being retrieved by the mobile unit, throughout the time intervals the average number at risk is the number present halfway through any one time interval if one assumes that patients are being admitted at a fairly constant rate. This assumption was true after the first hour. Thus from 1 hour onwards this column is equal to the number of patients present at the beginning of the time interval plus half of those entering the study during that time.

The fourth column shows the number of patients who died in the time interval; for section C, patients who arrested in the home are counted as deaths. The last column in sections B and C shows the 'expected no. of deaths' which is the proportion who died at that time in the community multiplied by the average number at risk. This is an estimate of the number of deaths which would occur in the patients at risk in the study group during each time interval if there was a similar proportion of deaths to that seen in the community.

Patients seen by the mobile unit within an hour of the onset of their symptoms were not seen at a constant rate; few were seen within the first 30 minutes because of the inevitable delays in calling the mobile unit. Indeed the average time for retrieval for patients seen at under 1 hour after the onset of symptoms was 43·6 minutes. Thus the average exposure time of the study group entering at under 1 hour was 43·6 to 60 minutes or 17·4 minutes. The 'average number at risk' in the third column is, therefore, $\frac{17{\cdot}4}{60} \times 47 = 13{\cdot}6$.

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Coronary artery vasospasm: the likely immediate cause of acute myocardial infarction

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SUMMARY Features of infarction can be divided into two types—the spasmodic and the mechanical. The former (pre-infarct angina and emotional factors in infarction) seem readily explainable by spasm, and are similar to the findings in angina which prompted Heberden to consider angina as spasmodic. The mechanical features of infarction (association with thrombosis and arteriosclerosis, and severe and unremitting chest pain) seem to be the antithesis of spasm and probably account for the reluctance to consider spasm seriously in infarction.

The injury-vasospasm hypothesis of acute myocardial infarction explains both spasmodic and mechanical features. Spasm represents a dominance of vasoconstricting over vasodilating forces. Coronary sclerosis can result in both ischaemia (vasodilating) and ischaemic injury-spasm (vasoconstricting). The fight-flight component of the autonomic nervous system is considered to be vasodilating, and the conservation-withdrawal portion to be vasoconstricting. Once spasm occurs, a new balance of forces obtains which can lead either to vasodilatation and relief of symptoms or to infarction.

Although there is growing interest in coronary artery vasospasm in acute myocardial infarction (Lange *et al.*, 1972; Cheng *et al.*, 1972; Hellstrom, 1973; King *et al.*, 1973; Khan and Haywood, 1974; Ciraulo, 1975; Chahine and Luchi, 1976; Engel *et al.*, 1976; Wiener *et al.*, 1976; Oliva and Breckinridge, 1977), the spastic origin of this disorder is not well accepted. In this discussion it will be proposed that vasospasm very likely initiates infarction.

There appears to be more evidence for spasm, albeit mostly circumstantial, than is generally realised. It will be argued that there has been a preconceived view that spasm is incapable of causing infarction and this has resulted in the neglect of readily accessible clinical evidence in favour of spasm, and in a disregard of inconsistencies in conventional pathogenetic concepts.

Angiographic evidence of spasm in infarction

Recently, in a few cases of infarction coronary artery spasm has been demonstrated angiographically (Cheng *et al.*, 1972; King *et al.*, 1973; Engel *et al.*, 1976; Wiener *et al.*, 1976). Such observations have not evoked strong support that spasm is the major cause of this disorder. Even though these are isolated cases, they seem important, as they associate spasm directly with muscle necrosis. As angiograms are taken only rarely during infarction, the few cases where spasm was shown provide little information as to the overall incidence of spasm with infarction. Importantly, spasm was recognised in 40 per cent of a recent series (Oliva and Breckinridge, 1977).

In addition, there are multiple observations of spasm in angina pectoris (Maseri *et al.*, 1977). This is accepted as indirect evidence for spasm in infarction, as infarction and angina are considered as one disorder, with myocardial necrosis representing an arbitrary division relating to the intensity and duration of spasm.

Spasmodic features of infarction—pre-infarct angina and emotional factors

Some attributes of infarction are similar to the findings in angina pectoris which prompted Heberden, who first described angina, to consider it as spasmodic. In his *Commentaries* (1802), he emphasised the character of the attack, the relation to emotional factors, and the occurrence of chest pain at rest. '. . . the access and recess of the fit is sudden . . ., it is increased by disturbances of the

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mind . . . (and) its attacks are often after the first sleep.'

This description resembles pre-infarct angina with features suggesting spasm. Pre-infarct angina often occurs at rest; this is also the major feature of variant angina for which a spastic origin is well documented (Higgins *et al.*, 1976; Maseri *et al.*, 1977). It seems reasonable that emotional factors and stress induce spasm by operating through the autonomic nervous system (Hellstrom, 1973, 1977).

The spasmodic features of myocardial infarction were recognised relatively recently. Emotional factors (Jenkins, 1976) were either minimised or totally neglected until 15 years ago (Russek, 1962), and while pre-infarct angina was described as early as 1937, it has been emphasised only in the past decade (Solomon *et al.*, 1969; Feinleib *et al.*, 1975). It was not until 1960 that Prinzmetal rediscovered than angina could occur at rest, and predicted a spastic origin.

In the mid-twentieth century, when spasm was unfashionable and spasmodic clinical features were not appreciated, those clinical characteristics of ischaemic heart disease were emphasised that matched the then accepted pathogenetic mechanisms. Descriptions of infarcts were confined to a discussion of the rapid onset of crushing, unremitting chest pain, a finding highly consistent with a sudden coronary thrombosis. Angina was described as occurring only with exertion, compatible with an origin from arteriosclerosis and relative vascular insufficiency. It might now be regarded as cautionary that spasm could have been considered an 'extravagant and improbable hypothesis' (Pickering, 1951).

Today, while spasmodic features of infarction are well described, they are usually ignored by those who believe exclusively in mechanical obstruction of coronary arteries. In addition, when discussed, it is only rarely that they are attributed directly to spasm (Burch and Giles, 1973; Hellstrom, 1973; Maseri *et al.*, 1977), probably because spasm had been declared irrelevant in infarction.

Deficiencies of nonspastic pathogenetic mechanisms of infarction

CORONARY ARTERY THROMBOSIS

The evidence that thromboses are secondary is convincing, especially the observation that their incidence is higher in the presence of infarcts which are one or more days old (Spain and Bradess, 1960). Some thrombi resemble postmortem clots (Hellstrom, 1971), suggesting a secondary development, and occur in vessels so constricted that their obstruction does not seem capable of causing infarction (Horn, 1963). Further, pre-infarct angina and the emotional component of infarction are not explained by thrombotic occlusions. However, a recent study group favoured the primacy of thrombosis (Chandler *et al.*, 1974). In any event, there is sufficient doubt to preclude belief in a primary role for thrombosis being used as convincing evidence against a vasospastic cause.

PLATELET AGGREGATION

This mechanism has been applied mainly to sudden coronary death (Schwartz and Gerrity, 1975), where platelet aggregates in intramyocardial arteries have been shown at necropsy (Haerem, 1972). However, experimentally, myocardial infarcts have followed adenosine diphosphate induced platelet aggregation (Mustard, 1972) and there is evidence of increased platelet stickiness in ischaemic heart disease (Frishman *et al.*, 1976). Platelet aggregates provide at least a theoretical explanation for spasmodic features of infarction, considering that stress causes intramyocardial platelet agglutination in rats (Haft and Fani, 1973) and pre-infarct angina might be explained by reversible platelet clumping.

The evidence for significant platelet clumping is not substantial, and there is little necropsy evidence for it in infarction. Moreover, platelet aggregates might be secondary events resulting from spasm itself, as coronary artery platelet aggregates have been found in dogs soon after experimental sudden partial coronary artery occlusion (Folts *et al.*, 1976). In addition, vascular injury (as would occur with spasm) itself probably induces platelet clumping (Mason *et al.*, 1977). Platelet aggregates might be secondary to infarction, as catecholamines and free fatty acids, which increase platelet stickiness (Taggart and Carruthers, 1971), are increased in infarction (Opie, 1975). The possibility of release of vasoconstrictive agents from aggregated platelets is discussed below.

DIRECT ARTERIOSCLEROTIC CAUSE OF INFARCTION

This concept assumes that the blood supply to the myocardium is limited by arteriosclerotic stenosis and myocardial necrosis is the result of relative ischaemia (Braunwald and Maroko, 1974).

The direct arteriosclerotic cause of infarction came into prominence shortly after the primacy of coronary thrombosis was questioned, and represents a significant modification of the classic cause of infarction. Previously, it was assumed that most infarcts were the result of coronary thrombosis, and only a minority resulted directly from coronary sclerosis, and then *only* in combination with shock, haemorrhage, etc. (Friedberg, 1967). The logic of a direct arteriosclerotic cause is not convincing. Many with severe coronary disease do not develop myocardial necrosis, and infarction can occur with patent arteries. If infarction is due directly to stenotic disease, how could an individual be capable of strenuous exercise immediately before an attack? And why do infarcts occur at rest? In addition, pre-infarct angina and the importance of emotional factors are inadequately explained by a direct arteriosclerotic cause.

The arteriosclerotic cause of infarction is associated closely with the concept of preservation of ischaemic myocardium. That pharmacological manipulation can improve survival of ischaemic myocardium in the dog after coronary artery ligation (Braunwald and Maroko, 1974) should not imply that infarction is caused by a fixed obstruction of coronary arteries.

Rebuttal to arguments that spasm cannot cause infarction

SCLEROTIC ARTERIES CANNOT UNDERGO SPASM

This concept was applied originally to angina (Keefer and Resnik, 1928; Blumgart *et al.*, 1940) and was a substantial reason for abandoning the notion of spasm in this disorder. While epicardial arterial spasm now is a recognised occurrence, most apparently consider that severely sclerotic arteries, as found in infarction and effort angina, cannot constrict. However, there is angiographic evidence that spasm occurs in infarction, in arteriosclerotic arteries in angina (Gensini, 1975; Maseri *et al.*, 1977), and even in effort angina (Chahine and Luchi, 1976). Though some sclerotic segments are probably too rigid to contract, it seems reasonable that spasm can involve vessels with significant disease. Rupture of coronary artery plaques implies violent vascular contractions (Leary, 1934; Hellstrom, 1977).

SPASM IS TOO MILD AND EVANESCENT TO CAUSE INFARCTION

Spasm in infarction has been rejected because of the lack of direct proof that it can cause myocardial necrosis (Arnett and Roberts, 1976). Further, in angina, spasm is a relatively mild and short lived event. These facts cannot preclude the possibility of spasm being severe or persistent enough to induce myocardial necrosis. The angiographic evidence of the association of spasm with infarction is at least suggestive that spasm can *cause* myocardial necrosis.

THERE IS LITTLE OR NO EXPERIMENTAL EVIDENCE FOR SPASM IN INFARCTION

One reason for the reluctance to accept an aetiological role for spasm in infarction is the sparsity of experimental data. This should not be taken as evidence against the hypothesis. There has been a lack of interest in pursuing spasm experimentally, and in recent years research workers have been preoccupied with the preservation of ischaemic myocardium.

SPASM CANNOT EXPLAIN ALL OF THE FEATURES OF INFARCTION (AND ANGINA)

Features of infarction can be divided into two types—the spasmodic and the mechanical. While the former (pre-infarct angina and emotional features) appear to be consistent with spasm, the mechanical attributes of infarction seem to be the antithesis of spasm. These include the association of infarction with arteriosclerosis and thrombosis, the severe and unremitting chest pain, and the persistence of the ischaemia during the early course of infarction. In addition, in effort angina, the onset of chest pain is related to the degree of exertion. Possibly intuitively, it has been felt that these mechanical aspects ruled out spasm, and this might be a major reason for the retention of current pathogenetic principles, no matter what their deficiencies.

Usually, those who stress the mechanical cause of infarction ignore the spasmodic features, and those who subscribe to spasm have not reconciled spasm with the mechanical features. A credible concept for the aetiology of infarction and effort angina should include an explanation for both types of features. Such an explanation might require viewing ischaemic heart disease from a different perspective.

The injury-vasospasm hypothesis of ischaemic heart disease

This concept explains both mechanical and spastic features of infarction and has been described elsewhere (Hellstrom, 1973, 1975, 1977). This abridged discussion will represent spasm as a dominance of vasoconstricting over vasodilating forces (Fig.).

The two major factors involved with infarction are arteriosclerosis and emotional stress. Arteriosclerosis is considered to cause chronic myocardial injury, which, in turn, incites injury-vasospasm. Conversely, arteriosclerosis induces ischaemia, which, via the anoxic-feedback mechanism of coronary autoregulation, is a potent vasodilator. If the injury reaction overwhelms the anoxic-feedback mechanism, spasm occurs.

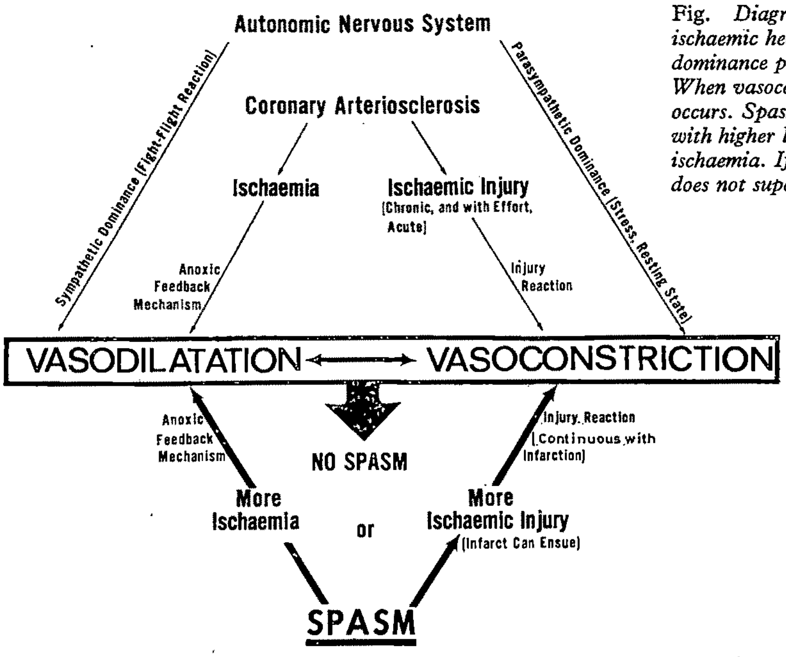
Autonomic Nervous System
Sympathetic Dominance (Fight-Flight Reaction)
Parasympathetic Dominance (Stress, Resting State)
Coronary Arteriosclerosis
Ischaemia
Ischaemic Injury (Chronic, and with Effort, Acute)
Anoxic Feedback Mechanism
Injury Reaction
VASODILATATION
VASOCONSTRICTION
Anoxic Feedback Mechanism
NO SPASM
Injury Reaction (Continuous with Infarction)
More Ischaemia
or
More Ischaemic Injury
(Infarct Can Ensue)
SPASM

Fig. *Diagram of major forces involved in ischaemic heart disease. Alpha-adrenergic dominance probably also is vasoconstricting. When vasoconstriction is dominant, spasm occurs. Spasm causes a new dynamic balance, with higher levels of ischaemic injury and ischaemia. If, at these new levels, vasodilatation does not supervene, infarction occurs.*

Emotional stress is related to the autonomic nervous system, which can effect coronary artery dilatation or constriction, and which might function in concert with the anoxic-feedback mechanism through neural reflexes. The anoxic-feedback mechanism is based in intramyocardial arteries, and the autonomic nervous system innervates both large and small coronary arteries. There is evidence that stress can induce an inappropriate parasympathetic response (Engel, 1971), and coronary artery constriction probably is caused by parasympathetic (Endo *et al.*, 1976) or alpha-adrenergic (Levene and Freeman, 1976) activity.

There are, undoubtedly, additional factors involved in the coronary vasodilative/vasoconstrictive balance. Irregular blood flow through a stenotic coronary segment might cause local injury-spasm. Prostaglandins cause both dilatation and constriction (Ogletree and Lefer, 1977), are involved in coronary autoregulation (Alexander *et al.*, 1975), and might influence the cardiac response to ischaemia (Berger *et al.*, 1976).

The hypothesis can be illustrated by applying it to clinical situations. In effort angina, the attack is the result of a combination of chronic ischaemic myocardial injury (arteriosclerosis) and acute ischaemic injury (effort), with the latter triggering the attack. A given amount of exertion usually is necessary to cause sufficient ischaemic injury to reach the threshold at which spasm is triggered. In all types of angina, once spasm occurs a new balance of forces obtains, because spasm causes higher levels of both ischaemia and ischaemic injury (Fig.). If, at the new levels, vasoconstriction continues to overbalance vasodilatation, infarction develops. However, the anoxic-feedback mechanism responds in proportion to the level of ischaemia, and it is likely that spasm usually results in the generation of sufficient vasodilative metabolites for self-correction. This is in keeping with the small fraction of attacks of angina which proceed to infarction. If spasm continues long enough for severe muscle injury and injury-spasm to develop, a different dynamic balance obtains, which favours the continuance of spasm and the development of infarction. Occasionally, effort angina is improved by further exertion (Lown, 1977). This apparent paradox is ascribed to an ascendency of vasodilative forces at the higher levels of ischaemia induced by effort, possibly abetted by a fight-flight autonomic nervous system response.

Coronary artery spasm caused by aggregated platelets

Instead of aggregated platelets directly causing intracoronary obstruction, it has been proposed recently that they cause coronary spasm by the release of vasoconstrictors such as the prostaglandin related thromboxane A2 (Oliva and Breckinridge, 1977). This approach to coronary spasm differs from the injury-vasospasm concept, where importance is placed on the injured myocardium and the direct coronary artery effect of the autonomic nervous system. In any event, the availability of more than one possible model for spasm should be advantageous.

The apparent reduction in sudden cardiac deaths with sulphinpyrazone, a prostaglandin inhibitor (Sherry, 1978), has been a major stimulus to the current interest in aggregated platelets. However, it is possible that the beneficial effects of sulphinpyrazone is not related to platelets and coronary arteries. The incidence of infarction in this study did not appear to be decreased significantly, and Frishman *et al.* reported in 1976 that reduction of platelet aggregability by prostaglandin inhibition did not affect angina. The reduced incidence of sudden cardiac death following treatment with sulphinpyrazone might be related to a decrease in ventricular fibrillation, and this arrhythmia occurs less frequently during experimental myocardial ischaemia after pretreatment with aspirin, one of whose actions is prostaglandin inhibition (Moschos *et al.*, 1978).

Therapeutic possibilities with a vasospastic cause of infarction

If, indeed, spasm initiates infarction, there are therapeutic possibilities beyond simple preservation of ischaemic myocardium. Vasodilators might abort the attack and during the acute stage of infarction might relieve spasm and reduce myocardial ischaemia (Hellstrom, 1975). The greatest potential might be in preventing infarcts. In addition to the obvious benefits in avoiding the acute attack and its complications, a major consideration is that acute coronary seizures may result in sudden death.

The adoption of fresh concepts of infarction may be useful in order to help prevent the attacks. Engel in 1977 suggested that, in medicine, the current biomedical model 'leaves no room within its framework for the social, psychological, and behavioral dimensions of illness' and should be replaced by a biopsychosocial model. While there are many published reports which detail the emotional side of infarction (Jenkins, 1976), this area is fairly isolated from the biomedical mainstream and overall receives inadequate attention, probably because of the lack of any notion of an integrating pathogenetic mechanism.

Proper attention should be paid to the early warnings of impending infarction and sudden coronary death. The high incidence of prodromata is well known (Feinleib *et al.*, 1975), but it is likely that the lack of a satisfactory explanation for their occurrence has inhibited a thoroughgoing approach to use recognition of these phenomena to prevent infarction. Relating tension and prodromata to spasm might encourage a more rational handling of the pre-infarct phase of myocardial infarction.

Table *Levels of acceptance of coronary artery spasm*

Coronary artery spasm does not exist
Spasm occurs only with catheter injury during angiograms
Spasm is real but associated only with variant angina
Variant angina is caused by spasm
Spasm is rarely shown in infarction
Spasm is more common than generally appreciated in infarction
Spasm is observed rarely in effort angina
Pre-infarct angina and infarction are caused by spasm
Effort angina is due to spasm

Acceptance of coronary artery spasm

Each year there has been an increased acceptance of coronary artery spasm (Vaisrub, 1976), and possible stages in this process are depicted in the Table. The current awareness varies from person to person, but the spastic cause of variant angina seems to be generally accepted. There is some interest in the possibility of spasm in infarction, but little for effort angina.

The possibility, or even probability, that spasm initiates infarction is now a tenable concept.

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Correlation of ejection fraction and infarct size estimated from the total CK released in patients with acute myocardial infarction

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SUMMARY In order to investigate the relation between infarct size in acute myocardial infarction and left ventricular ejection fraction early after recovery, total creatine kinase released was calculated by the modified method of Sobel *et al.* (1972) from the serial determinations of serum CK activity; left ventriculography and selective coronary arteriography were performed at a mean of 2 months after the onset of infarction in 34 patients with acute myocardial infarction. Of 34 patients, 32 (94%) had left ventricular asynergy. In 21 patients with akinesis and/or dyskinesis, a significant correlation was found between the extent of the non-contracting segment of the left ventricle and left ventricular ejection fraction, indicating that the extent of the non-contracting segment contributes largely to reduction of ejection fraction in patients with myocardial infarction.

A close inverse correlation was also observed between the infarct size and ejection fraction after anterior and after inferior infarction, though cardiac index was maintained over 2·0 l/min per m^2 in all except 3 patients. The ejection fraction in patients with anterior myocardial infarction was lower than in those patients with inferior myocardial infarction with comparable values of total CK released. This was true even after exclusion of 6 patients with proximal right coronary artery lesions who might have had right ventricular necrosis as well as left, indicating that left ventricular function after infarction depends in part on the site of the infarct.

Since Harrison (1965) reported that left ventricular asynergy was one of the major factors determining cardiac function in ischaemic heart disease, the unfavourable effects of asynergy on left ventricular function have been studied extensively. Klein *et al.* (1967) showed that left ventricular end-diastolic volume is much increased when aneurysm comprises 20 to 25 per cent of the ventricular surface. Feild *et al.* (1972) also reported a close relation between the extent of akinesis and left ventricular ejection fraction in patients who had had a previous myocardial infarction. Rogers *et al.* (1977) reported that infarct size estimated from total creatine kinase (CK) released was related directly to the area of the abnormally contracting segment and to ejection fraction, but the relation between the extent of myocardial ischaemia or necrosis causing asynergy and left ventricular function required further investigation.

In the present study, we attempted to estimate infarct size by calculating the total CK released from infarcted myocardium using the method of Sobel *et al.* (1972) in patients with acute myocardial infarction and to relate this to left ventricular ejection fraction, cardiac index, and left ventricular end-diastolic pressure (LVEDP), measured after healing of the infarct.

Subjects and methods

Thirty-four patients (29 men and 5 women), admitted to the Sakurabashi Watanabe Hospital with acute myocardial infarction within 12 hours of the onset of chest pain and surviving for more than 4 weeks, were included in this study. Their ages ranged

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from 35 to 71 years (mean 54·4 years). Eighteen patients had anterior infarction and 16 inferior infarction. Four patients gave a history of previous myocardial infarction (anterior in 2 patients and inferior in 2 patients). The clinical diagnosis was established by a history of typical chest pain, new Q waves on the electrocardiogram, and increased serum levels of CK, aspartate aminotransferase, α-hydroxybutyric dehydrogenase, and lactic dehydrogenase.

Patients with cardiogenic shock or severe arrhythmia and those who were given beta-blockers or digitalis, which affect myocardial contractility, were excluded.

ESTIMATION OF TOTAL CK RELEASED (ΣCK)

In all patients, peripheral venous blood for CK determination was taken at 4-hourly intervals for the first 24 hours and then at 6-hourly intervals until CK activity returned to near-normal levels (approximately 40 IU/ml). The serum was separated within 2 hours of clotting and stored at 4°C. The determinations were made within 15 hours of sampling by the modified method of Nuttal-Wedin (Nuttal and Wedin, 1966), with a normal range of less than 40 IU/ml. As intramuscular injections can cause release of CK, all injections were given either intravenously or subcutaneously.

The appearance function of CK released from the injured heart muscle was calculated according to the method of Sobel *et al.* (1972) modified by Norris *et al.* (1975). The principle of this method is that the instantaneous rate change in serum CK activity (dE(t)/dt) reflects the rate of appearance of enzyme released from the injured myocardium into the circulation (f(t)) and also its disappearance from the circulation in monoexponential fashion as represented by the disappearance rate (K) multiplied by the instantaneous serum CK activity (E(t)).

$$\frac{dE(t)}{dt} = f(t) - K.E(t)$$

Thus, the appearance function is obtained as follows:

$$f(t) = \frac{dE(t)}{dt} + K \cdot E(t),$$

where E(t) represents the instantaneous serum CK activity, after subtracting the individual basal serum CK activity (average 15 IU/ml). The CK disappearance rate (K) was estimated in each patient from the terminal portion of the disappearance curve (E(t)) plotted semilogarithmically. Integration of the appearance function ($\int_0^t f(t)dt$) theoretically should give the total amount of CK released per unit of blood volume (ΣCK): this has been shown by Shell *et al.* (1971) to be closely correlated to infarct size.

CATHETERISATION AND ANGIOGRAPHIC PROCEDURES

Right and left heart catheterisation and left ventriculography were performed 1 to 5 months (average 2·1 months) after the onset of infarction; patients were premedicated with oral diazepam (10 mg), subcutaneous atropine sulphate (0·5 mg), and intramuscular hydroxyzine (50 mg). After measurement of cardiac output by the dye dilution method, a 30° right anterior oblique left ventriculogram was obtained after injection of 40 to 50 ml sodium diatrizoate, with exposure of 60 frames/s on 35 mm film.

The outline of the left ventricle at end-systole and end-diastole was traced from individual cine frames projected on to a film motion analyser. Only normally conducted contractions were analysed, and post-extrasystolic beats were omitted. End-systolic and end-diastolic volumes were determined by using the area-length method of Sandler and Dodge (1968). The ejection fraction was determined by dividing the stroke volume (end-diastolic volume minus end-systolic volume) by the end-diastolic volume.

Ventricular wall motion was also assessed by analysis of the ventricular silhouette throughout a cardiac cycle. Asynergy was classified using the criteria of Herman and Gorlin (1969). In order to define localised segments of abnormal ventricular contraction, end-diastolic and end-systolic outlines of the left ventricular chamber for a single beat were superimposed, and akinetic or dyskinetic segments were identified. The length of the end-diastolic ventricular perimeter (circumference) and the length of the akinetic or dyskinetic segment of the end diastolic perimeter were determined with a map measurer. The ratio of the extent of the non-contracting segment of the left ventricle to the total end-diastolic circumference of the left ventricle (NCS %) was also calculated in the patients with akinesis or dyskinesis, in order to study the relation between left ventricular ejection fraction and the extent of the non-contracting segment (Fig. 1).

Results

TOTAL AMOUNT OF CK RELEASED (ΣCK) AND ASYNERGY

The Table shows the relation between the degree of asynergy and the total amount of CK released (ΣCK), which is closely related to infarct size. Mean total amount of CK released in 18 patients with anterior infarction and in 16 patients with inferior infarction was 1011·8 ± 110·5 IU/ml (mean ± SE)

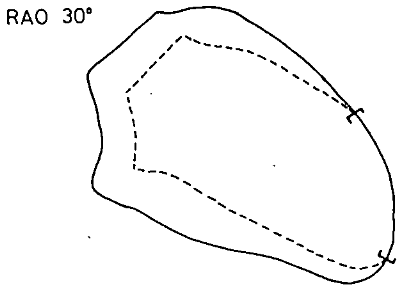

Fig. 1 *Measurement of the extent of non-contracting segment (NCS).*
NCS (%) = length of akinetic or dyskinetic segment of end-diastolic circumference/total end-diastolic circumference × 100.

Table *Total CK released (ΣCK) and the degree of asynergy in 34 patients with acute myocardial infarction*

Infarct site	*Asynergy*	*No. of cases*	*ΣCK (IU/ml)* *mean ± SE*
Anterior	Normal	0	
	Hypokinesis	2	532·0 ± 112·4
	Akinesis	8	955·3 ± 170·6
	Dyskinesis	8	1188·4 ± 143·0
Inferior	Normal	2	638·5 ± 260·6
	Hypokinesis	8	1161·3 ± 119·0
	Akinesis	6	1106·6 ± 121·9
	Dyskinesis	0	

and 1058·6 ± 98·2 IU/ml, respectively; the difference was not statistically significant.

Of 34 patients, 32 (94%) had left ventricular asynergy with hypokinesis, akinesis, or dyskinesis. Eight of 18 patients with anterior infarction had dyskinesis, 8 had akinesis, and 2 had hypokinesis. The mean total amount of CK released in 8 patients with dyskinesis was 1188·4 ± 143·0 IU/ml, which was greater than that released in 8 patients with akinetic wall movement (955·3 ± 170·6 IU/ml) (Table). Of 16 patients with inferior infarction, 6 had akinesis, 8 had hypokinesis, and 2 had normal wall movement. There was no significant difference in mean total CK released (ΣCK) between patients with akinesis and those with hypokinesis. However, in inferior infarction mean total CK released in 14 patients with akinesis or hypokinesis was 1117·8 ± 88·3 IU/ml and which was significantly ($P < 0·01$) greater than that (870·6 ± 148·3 IU/ml) in 10 patients with anterior infarction and akinesis or hypokinesis. This suggests that the degree of asynergy, as assessed by left ventriculography, is less in patients with inferior infarction than in those with anterior infarction with the same infarct size.

In 20 of 22 patients without previous myocardial infarction who had akinesis or dyskinesis (14 patients with anterior infarction, 6 patients with inferior infarction), there was a significant correlation ($r = 0·68$, $P < 0·01$) between the total amount of CK released (ΣCK) and the extent of the non-contracting segment of the left ventricle (NCS %) (Fig. 2). Furthermore, in 2 patients with previous myocardial infarction, the non-contracting segment of the left ventricle was larger than in those without previous myocardial infarction at the same values of total CK released (Fig. 2).

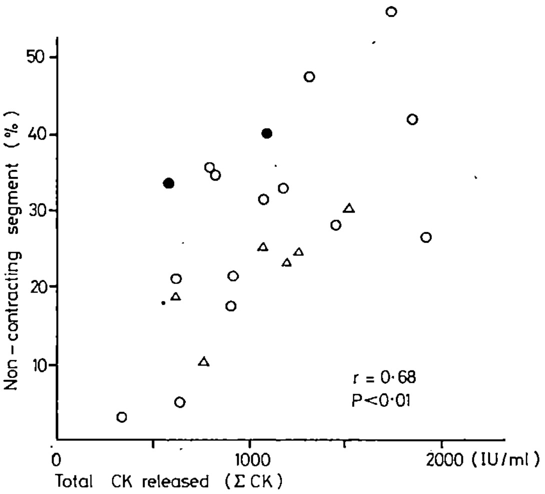

Fig. 2 *Correlation between the total CK released (ΣCK) and the extent of the non-contracting segment ($r = 0·68$, $P < 0·01$) ○: anterior infarction without previous infarction, ●: anterior infarction with previous infarction, △: inferior infarction without previous infarction.*

TOTAL CK RELEASED (ΣCK) AND EJECTION FRACTION

Close inverse correlations were found between the total CK released and the ejection fraction both in 18 patients with anterior infarction and in 16 patients with inferior infarction (Fig. 3). The ejection fraction was lower in the patients with anterior infarction than in those with inferior infarction with comparable values of total CK released. Though in the patients with a proximal right coronary artery lesion, part of the CK release may not be from the left ventricle (Rogers *et al.*, 1977), this difference in ejection fraction between patients with anterior and inferior infarction is also evident if the 6 patients with significant right coronary lesions proximal to

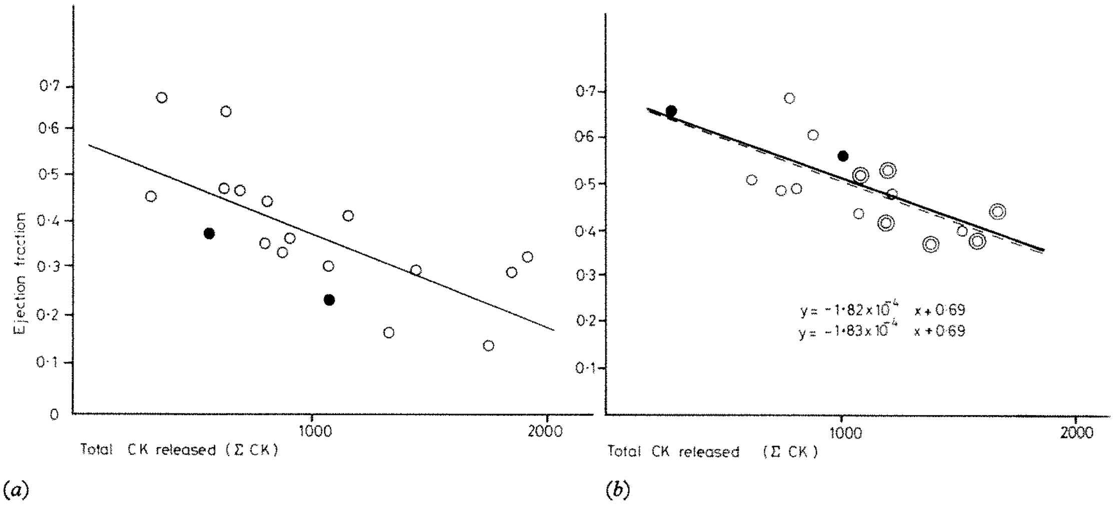

Fig. 3 (*a*) *Left ventricular ejection fraction and total CK released (ΣCK) in 18 patients with anterior infarction ($r = -0{\cdot}71$, $P < 0{\cdot}01$). ○: patients without previous infarction, ●: patients with previous infarction.* (*b*) *Left ventricular ejection fraction and total CK released (ΣCK) in 16 patients with inferior infarction ($r = -0{\cdot}73$, $P < 0{\cdot}01$). The dotted regression line excludes 5 patients with proximal right coronary artery lesions. ○: patients without previous infarction, ●: patients with previous infarction, ◎patients with proximal right coronary artery lesions.*

the origin of the marginal branch are excluded (Fig. 3b). Furthermore, as shown in Fig. 4, there was a close inverse correlation between the extent of the non-contracting segment of the left ventricle and ejection fraction ($r = -0{\cdot}80$, $P < 0{\cdot}01$) in 19 patients without previous myocardial infarction who had akinesis or dyskinesis, indicating that the extent of the non-contracting segment contributes to the reduction of the ejection fraction in patients with myocardial infarction.

TOTAL CK RELEASED, CARDIAC INDEX, AND LEFT VENTRICULAR END-DIASTOLIC PRESSURE

There is no significant correlation between the total amount of CK released and the cardiac index, and in 30 out of 33 patients the cardiac index was maintained over 2·0 l/min per m^2 (Fig. 5). No significant difference in cardiac index was found between patients with anterior infarction and those with inferior infarction. As shown in Fig. 6, an increase

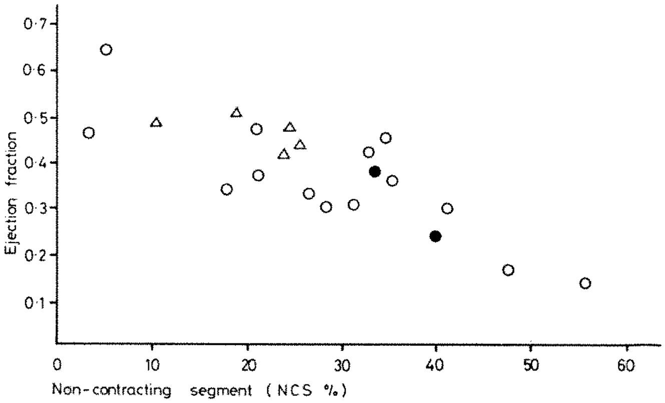

Fig. 4 *Correlation between the extent of the non-contracting segment (NCS%) and left ventricular ejection fraction ($r = -0{\cdot}80$, $P < 0{\cdot}01$). Symbols as in Fig. 2.*

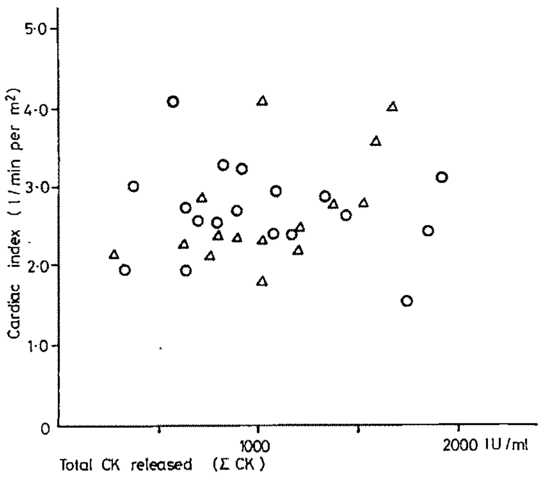

Fig. 5 *Cardiac index and total CK released (ΣCK). Symbols as in Fig. 2.*

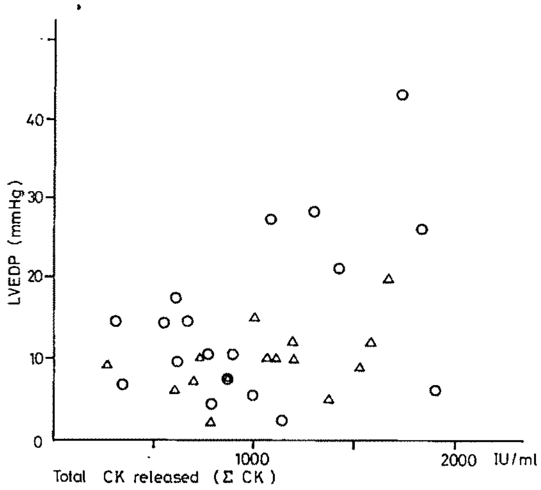

Fig. 6 *Left ventricular end-diastolic pressure (LVEDP) and total CK released (ΣCK). Symbols as in Fig. 2.*

in the total CK released was, however, often associated with an increase in left ventricular end-diastolic pressure, though higher left ventricular end-diastolic pressure was observed in patients with anterior infarction than in those with inferior infarction at the same level of the infarct size.

Discussion

Since Tennant and Wiggers (1935) first described the paradoxical movement of an area of left ventricular myocardium in the dog after ligation of the coronary artery supplying that area, many investigators have found that regional myocardial function greatly influences global myocardial function in patients with ischaemic heart disease. Harrison (1965) observed that the lack of uniform coordinated left ventricular contraction assessed by left ventriculography greatly altered left ventricular function in the patients with ischaemic heart disease. Though there have been many studies of the effect of asynergy on left ventricular function (Klein *et al.*, 1967; Baxley and Reeves, 1971; Baxley *et al.*, 1971), few investigators have attempted to relate asynergy and the extent of the myocardial ischaemia or necrosis, which probably causes the asynergy, to overall left ventricular function (Mathey *et al.*, 1975; Rogers *et al.*, 1977). In the present study, we assessed infarct size by calculating the total CK released from infarcted myocardium by a previously reported method (Inoue *et al.*, 1977) in patients with acute myocardial infarction, and related this to the indices of left ventricular function such as left ventricular ejection fraction, cardiac index, and left ventricular end-diastolic pressure measured early after recovery from the disease.

(i) VALIDITY OF MEASUREMENTS

Estimation of infarct size

In this investigation, we estimated the infarct size by the method of Sobel *et al.* (1972) as modified by Norris *et al.* (1975) from serial determinations of serum CK activity. Though this method is considered the most sensitive one for the estimation of infarct size (Sobel *et al.*, 1972; Norris *et al.*, 1975), there are several problems in its clinical application (Roe and Starmer, 1975). The most important of these is the influence of a release of CK of non-cardiac origin on serum CK activity. In our study, in order to avoid the effect of extracardiac CK release possibly from skeletal muscle, all injections were given either intravenously or subcutaneously. Patients with profound haemodynamic changes associated with cardiogenic shock and/or severe arrhythmias, which could also cause a release of extracardiac CK, were excluded. Two patients who underwent right heart catheterisation using a Swan-Ganz catheter during the acute phase of infarction were not excluded, because no increase in serum CK activity after this procedure had been observed in our previous study (Hori *et al.*, 1976).

The second problem is that the calculated value of total CK release from infarcted myocardium may be affected by changes in the volume of CK distribution space during the period of CK release. Witteveen *et al.* (1976) recently reported the influence of plasma volume change on calculated infarct size, suggesting that changes in plasma volume should be taken into account when infarct size is calculated from serum levels. However, patients with cardiogenic shock and/or those requiring large infusions, in whom plasma volume was changing during release of CK from infarcted myocardium, were excluded; it is unlikely that total CK released was significantly affected by small changes in plasma volume in patients included in the study.

The final problem concerns the variability of the disappearance rate of CK activity from the circulation. Roberts *et al.* (1975) showed that haemodynamic disturbances did not greatly affect the disappearance rate of CK activity in the conscious dog. However, Norris *et al.* (1975) reported large individual differences in disappearance rates of CK activity. Following their suggestion, we estimated the disappearance rate of CK activity in each patient.

ESTIMATION OF ASYNERGY AND LEFT VENTRICULAR EJECTION FRACTION

In this presentation, we estimated the degree and extent of asynergy and left ventricular ejection fraction from the single plane left ventriculogram (RAO 30°). Miller *et al.* (1974) examined the biplane left ventriculograms (RAO 30° and LAO 60°) of 123 consecutive patients with arteriographically proven coronary arterial stenosis for abnormalities of left ventricular segment contraction. They observed that the 30° right anterior oblique view was adequate for detecting a disorder in contraction pattern except in the patients with posterior infarction. Furthermore, in their study they also found that asynergy was not observed in the left anterior oblique view when it was not observed in the right anterior oblique projection. Other investigators reached the same conclusions (Cohn *et al.*, 1972; Williams *et al.*, 1973).

A second problem is the difference between estimates of left ventricular ejection fraction made from biplane and from single plane left ventriculograms. Cohn *et al.* (1974) reported that there was no significant difference in ejection fraction derived from biplane and single plane left ventriculograms in 42 patients with coronary heart disease (mean values 0·55 and 0·52, respectively). Furthermore, in the 27 patients who had asynergic ventricles, the biplane values for ejection fraction were also not significantly different from the single plane values (mean values 0·46 and 0·41, respectively). Though the minor axes of the left ventricle in the right and left anterior oblique projections often differed by several millimetres, with the left anterior oblique measurement usually larger, this difference was seen at end-systole and at end-diastole, in both small and large hearts, and in patients with and without asynergy; differences between ejection fractions calculated in the two projections were not significant (Cohn *et al.*, 1974).

Finally, because of the effect of contrast material on left ventricular function, we performed left ventriculography before selective coronary arteriography.

(ii) TOTAL CK RELEASED AND LEFT VENTRICULAR FUNCTION

Although we observed a close inverse correlation between the total CK released and left ventricular function, several problems have to be considered in assessing the relation between the total CK released and left ventricular function.

The first problem is that left ventricular function could change in the course of myocardial infarction. Pairolero *et al.* (1970) made serial estimations of left ventricular ejection fraction in the conscious dog after ligation of a coronary artery, and reported that the ejection fraction fell after ligation but rose to a steady level one month later. Karsner and Dwyer (1916) in canine studies reported that replacement of the infarcted myocardium by scar tissue was not established until 16 days after ligation of the coronary artery, while complete scar formation had not occurred until 61 days after the ligation. Mallory *et al.* (1939) also reported that development of an infarcted scar in man was not complete until about 2 months after the onset. In this study we performed left ventriculography 1·0 to 5·0 months (average 2·1 months) after the onset of infarction, when left ventricular function was stable.

The second problem concerns the relation between the total CK released and asynergy. Miller *et al.* (1974) assessed the relation between electrocardiographic abnormality and segmental abnormality of left ventricular contraction as shown by the left ventriculogram in 77 patients with electrocardiographic evidence of transmural myocardial infarction. They showed that of these 77 patients with infarction, 73 (95%) had a localised contraction abnormality, a finding which is consistent with ours (31 of 33 patients, 94%). However, myocardial infarction is not always associated with abnormal movement of the ventricular wall (Master *et al.*, 1940) and the extent and severity of myocardial infarction as well as regional abnormalities of ventricular contraction influence left ventricular function. We showed that the extent of the akinetic or dyskinetic segment was closely correlated with left ventricular ejection fraction ($r = -0{\cdot}80$, see Fig. 4) and this was consistent with the experience of other authors (Feild *et al.*, 1972; Kitamura *et al.*, 1972; Rogers *et al.*, 1977). Furthermore, it is interesting that the total CK released closely correlated with the ejection fraction, as Rogers *et al.* (1977) have recently reported (anterior infarction: $r = -0{\cdot}71, P < 0{\cdot}01$; inferior infarction: $r = -0{\cdot}73$, $P < 0{\cdot}01$). In our study, 10 patients with hypokinesis and 2 patients with normal ventricular contraction were included and there was still a close correlation between the total CK released and ejection fraction, suggesting that the extent of the infarct greatly influenced left ventricular function even when there was no akinesis or dyskinesis.

The third problem is the relation between the site of infarction and left ventricular function. In our study, the ejection fraction in the patients with anterior infarction was lower than in those with inferior infarction with the same values of total CK released (see Fig. 3). On the other hand, in both anterior and inferior infarction total CK released in patients with hypokinesis was less than that in those with akinesis or dyskinesis. The severity of asynergy on left ventriculography in patients with inferior infarction was less than in those with anterior infarction with comparable levels of total CK released (see Table). Rogers *et al.* (1977) recently reported that the total CK released correlated with the ejection fraction ($r = -0{\cdot}78$) and that there was no difference between anterior and inferior infarction except in 2 patients with proximal right coronary lesions, who had disproportionately high left ventricular ejection fractions probably because of the extent of right ventricular infarction. We therefore derived the regression lines relating the ejection fraction to total CK released in patients with inferior infarction both including and excluding 6 patients with proximal right coronary lesions (Fig. 3b); these were not significantly different. This indicates that the higher ejection fraction in patients with inferior infarction is the result of other factors than the presence of infarction not involving the left ventricle.

Two possible causes for the difference between anterior and inferior infarction can be considered. The first possibility is that the asynergy in patients with inferior myocardial infarction is less extensive than in patients with anterior infarction even with the same infarct size. Miller *et al.* (1974) assessed the asynergy by biplane left ventriculography in 49 patients with myocardial infarction and observed that dyskinesis was more frequent in the patients with anterior infarction than in those with inferior infarction, while hypokinesis was more frequent in inferior infarction than in anterior infarction. In our series, only 2 of 18 patients with anterior infarction had hypokinesis, while 2 of 16 patients (12·5%) with inferior infarction had a normal contraction pattern and 8 patients (50%) had hypokinesis. Furthermore, Miller *et al.* (1974) also reported that the area of asynergy of the left ventricle in 21 patients with anterior infarction was 42 per cent and this value was significantly larger than that (23%) in 28 patients with inferior infarction. Russel *et al.* (1973) studied haemodynamics in 50 patients with acute myocardial infarction and showed that patients with anterior infarction had significantly greater left ventricular filling pressures ($P < 0{\cdot}05$) than those with inferior infarction. These findings strongly suggest that the severity and extent of asynergy and left ventricular function depend partly on the site of infarct.

The second possibility is that this difference results from the underestimation of ejection fraction in patients with inferior infarction consequent upon the use of single plane left ventriculography (RAO 30°). Though some part of the inferior and posterior wall movement cannot be detected on single plane ventriculograms, the difference between left ventricular volumes measured from single plane and biplane left ventriculograms was reported to be less than 7 per cent. It thus seems that the first possibility is more likely than the second.

Although we found a decreased ejection fraction in all patients with myocardial infarction, the cardiac index was more than 2·0 l/min per m^2 in all except 3 patients. It has been reported in previous studies that in spite of a depressed ejection fraction, the cardiac index is often maintained within the normal range during the recovery phase of myocardial infarction; this compensation is probably mediated by the Frank-Starling mechanism (Soloff, 1968; Baxley *et al.*, 1971). In our study we noted that patients with a large infarct had a high left ventricular end-diastolic pressure, and deduced that increased ventricular contraction resulted from increased preload.

(iii) ESTIMATION OF FUNCTION OF NON-INFARCTED AREA

Feild *et al.* (1972) evaluated function of the non-infarcted area in patients with ischaemic heart disease by studying the relation between the extent of the non-contracting area and the ejection fraction. A patient with hypothyroidism who was excluded from our study showed a disproportionately low ejection fraction (0·19) compared with the total CK released (715 IU/ml); this suggested that contractility in the non-infarcted area was depressed by the hypothyroid state, the predicted ejection fraction being 0·44.

It may thus be possible to estimate the function of the non-infarcted area by relating total CK released to the measured ejection fraction. When a measured ejection fraction is lower than that predicted from total CK released, it is likely that function of the non-infarcted myocardium is impaired.

This information may be useful for the prediction of prognosis and the planning of treatment.

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Patterns of haemodynamic alteration during left ventricular ischaemia in man

Relation to angiographic extent of coronary artery disease[1]

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SUMMARY Haemodynamic changes produced by rapid atrial pacing (60 patients, 52 of whom developed angina) or in association with spontaneous angina (32 patients) were measured in 92 patients with angiographic coronary artery disease. The extent of coronary artery disease was scored by the jeopardy score system (range 0 to 12). The haemodynamic changes induced by ischaemia occurred in 3 patterns: pattern I, no change in filling pressure or in mean systemic arterial pressure; pattern II, a rise in filling pressure and a rise in mean systemic arterial pressure; pattern III, a rise in filling pressure, but no significant change or a fall in mean systemic arterial pressure. In patients who had a pattern II or a pattern III response to ischaemia, the change in mean systemic arterial pressure was linearly related to the corresponding change in cardiac output. The likelihood of a patient showing a given pattern of ischaemia-induced haemodynamic change was related to the extent of coronary artery disease: of 22 patients with jeopardy scores of 2 or 4, 91 per cent exhibited pattern I, 9 per cent pattern II, and none pattern III; of 39 patients with jeopardy scores of 6 or 8, 40 per cent exhibited pattern I, 22 per cent pattern II, and 38 per cent pattern III; of 31 patients with jeopardy scores of 10 or 12, 12 per cent exhibited pattern I, 10 per cent pattern II, and 78 per cent pattern III ($P < 0{\cdot}01$). Among the 54 patients in whom serial cardiac output determinations were available, a decline of the left ventricular function curve during ischaemia was demonstrable in 8 per cent of those with a pattern I response, in 54 per cent of those with a pattern II response, and in 90 per cent of those with a pattern III response ($P < 0{\cdot}01$). The pattern of response was unrelated to resting angiographic left ventricular ejection fraction, whether ST segments became elevated or depressed, or whether ischaemia was pacing-induced or spontaneous. These results suggest that the haemodynamic response to ischaemia is determined by the fraction of the left ventricle that becomes dysfunctional during ischaemia.

Left ventricular ischaemia accompanying spontaneous angina, exercise-induced angina, and angina induced by rapid atrial pacing has been shown to be associated in some patients with an acute rise in left ventricular filling pressure, which may precede, accompany, or follow the onset of chest pain (Müller and Rørvik, 1958; Parker *et al.*, 1969; Barry *et al.*, 1976). A rise in systemic arterial blood pressure is also an accompaniment of angina in some patients (Roughgarden and Newman, 1966; Littler *et al.*, 1973). The extent and pattern of haemodynamic alteration during ischaemia varies from patient to patient, however. Not all patients undergoing haemodynamic monitoring during angina have shown changes in left ventricular filling pressure (Cannom *et al.*, 1974; Lecerof, 1974), and, in some patients, systemic blood pressure has not changed or has even fallen (Cohen *et al.*, 1965; Thomson and Kelemen, 1975). The determinants of the

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haemodynamic response to left ventricular ischaemia are unknown.

The goal of the present study is to examine the relation between the angiographic extent of coronary artery disease and the haemodynamic changes occurring with ischaemia and, moreover, to assess whether this relation is modified by the state of resting left ventricular function.

Methods

PATIENTS

The study population, 97 patients, consists of 2 separate groups. In the first group, 65 patients, rapid atrial pacing was performed as part of the cardiac catheterisation procedure. These patients all had a history of recurrent chest pain and had been referred for coronary angiography. In the second group, 32 patients with recurrent angina at rest, haemodynamic and electrocardiographic measurements were recorded during episodes of spontaneous angina. Thirty of the patients with recurrent spontaneous angina at rest underwent electrocardiographic and haemodynamic monitoring in our coronary care unit as part of the clinical management of unstable angina, and 2 patients had electrocardiographic and haemodynamic measurements recorded during an episode of spontaneous angina in the cardiac catheterisation laboratory.

HAEMODYNAMIC AND ELECTROCARDIOGRAPHIC MEASUREMENTS

(*1*) *Pacing study group*

The cardiologist who referred the patients for catheterisation often had specifically requested that the pacing study be performed for clinical purposes; in all other cases the patients were asked for informed consent to perform an atrial pacing study as part of the cardiac catheterisation procedure.

Propranolol and isosorbide dinitrate were withheld on the day of the procedure until cardiac catheterisation was completed. Systemic arterial blood pressure was measured by means of a radial artery cannula. A temporary pacing electrode was positioned to achieve high right atrial pacing. Left ventricular pressures or pulmonary artery pressures were recorded by means of saline-filled catheters. Left ventricular end-diastolic pressure was measured at the nadir of the post-A pressure just before the rapid upstroke of the left ventricular systolic pressure; when identification was difficult, the end-diastolic pressure was assumed to correspond to the peak of the electrocardiographic R wave. Left ventricular stroke work (joules) was defined as [stroke volume] × [mean arterial pressure—left ventricular filling pressure]. Cardiac output determinations were performed in duplicate by an indicator dilution method (indocyanine green injection in right atrium, sampling from radial artery).

The pacing procedure was carried out before angiographic procedures. Resting measurements of left ventricular filling pressure (measured as left ventricular end-diastolic pressure in 59 patients and as pulmonary wedge pressure in 6 patients), mean systemic arterial pressure, cardiac output, and the electrocardiogram (leads III and V4) were recorded. Atrial pacing was then begun 10 to 20 beats/min higher than the patient's resting heart rate, and the pacing rate was increased in increments of 10 beats/min for one minute each until either angina occurred, atrioventricular block developed, or until a rate of 150/min was reached (a few patients were paced up to as high as 172 beats/min). The highest pacing rate was maintained for 2 minutes whereupon left ventricular filling pressure, mean systemic arterial pressure, electrocardiogram, and cardiac output determinations were recorded, and, subsequently, the pacemaker was turned off. At the offset of pacing, the left ventricular filling pressure was continuously recorded for approximately 20 beats. Three minutes after pacing was discontinued, left ventricular filling pressure, mean systemic arterial pressure, electrocardiogram, and cardiac output measurements were repeated.

The change in mean systemic arterial pressure, change in cardiac output, and change in stroke volume produced by pacing were calculated by comparing values measured at the highest pacing rate with corresponding values measured in the baseline state. The baseline values were taken either as those measured before pacing or as those measured 3 minutes after pacing, whichever gave the smallest differences compared with values at the highest pacing rate. The baseline values were defined in this way because the institution of pacing in itself sometimes resulted in fluctuations of the mean systemic arterial pressure, apparently because of the patient's attendant anxiety that bore no relation to whether or not ischaemia subsequently developed.

The change in the left ventricular filling pressure produced by pacing is defined as the difference between the baseline left ventricular filling pressure and the left ventricular filling pressure at the offset of pacing (average of the second to the eleventh post-pacing beats), unless ventricular function curves are being referred to (see below).

(*2*) *Spontaneous angina group*

Thirty patients with unstable angina had had balloon-tipped pulmonary artery catheters and radial artery cannulae inserted in the coronary care unit to facilitate their clinical management. Angina occurred while the patients were resting in bed and while many were receiving varying combinations of propranolol, sublingual or oral isosorbide dinitrate, and cutaneous glyceryl trinitrate paste. In addition, 6 patients were undergoing intra-aortic counterpulsation at the time that angina occurred. Left ventricular filling pressure (pulmonary wedge pressure) and mean systemic arterial pressure were recorded during the patient's subjective complaint of chest pain, but before the administration of glyceryl trinitrate, and were compared with measurements made before pain. Cardiac output was determined before and during angina in 13 patients (indocyanine green or thermal dilution; variability in duplicate determinations of cardiac output by thermal dilution 10%). Pulmonary artery and systemic blood pressures were recorded continuously while haemodynamic monitoring was performed. Pre-angina cardiac output determinations were made during a pain-free interval that was remote from administration of glyceryl trinitrate while the patient was on the same therapeutic regimen as that present at the time of angina. Angiographic procedures were performed during the same hospital admission. In no case was myocardial infarction known to occur between the time of the spontaneous angina episode when haemodynamic measurements were made and the time of subsequent angiographic procedures. An additional 2 patients had episodes of spontaneous angina in the catheterisation laboratory; left ventricular end-diastolic pressure and mean systemic arterial pressure during angina were compared with their pre-angina values.

Haemodynamic and electrocardiographic data for a single angina episode per patient are reported. Haemodynamic data surrounding only one episode of angina were available in 29 patients; in the other 3 patients, the pressure data that correspond to the episode during which cardiac output determinations were available were chosen as representative.

DEFINITION OF ISCHAEMIA-INDUCED DECLINE IN VENTRICULAR FUNCTION CURVE

In the present study, the left ventricular filling pressure and cardiac output were measured together at two points: a baseline state, when left ventricular ischaemia was absent by clinical and electrocardiographic criteria, and during rapid pacing or spontaneous angina, when the degree of ischaemia was to be assessed. Depression of the ventricular function curve during pacing or during spontaneous angina is defined as either a fall in stroke work at an unchanged or higher ventricular filling pressure or as no change in stroke work when the left ventricular filling pressure rises. When ventricular function curves were assessed in pacing-induced ischaemia, the change in the left ventricular filling pressure was measured as the difference between baseline left ventricular filling pressure and the left ventricular filling pressure at the highest pacing rate.

ANGIOGRAPHIC DATA

All 97 patients underwent selective coronary angiography. All angiograms were reviewed by one observer. The coronary circulation was considered as 6 arterial segments. Each arteriogram was assigned a score, termed the jeopardy score (Dash *et al.*, 1977), which expresses how many of the 6 segments are jeopardised, directly or indirectly, by significant proximal obstruction. The 6 arterial segments and the principle of the jeopardy score are illustrated in Fig. 1. Two points are counted for each segment jeopardised. Thus, the jeopardy score ranged from 0 (a patient with no significant coronary lesions) to

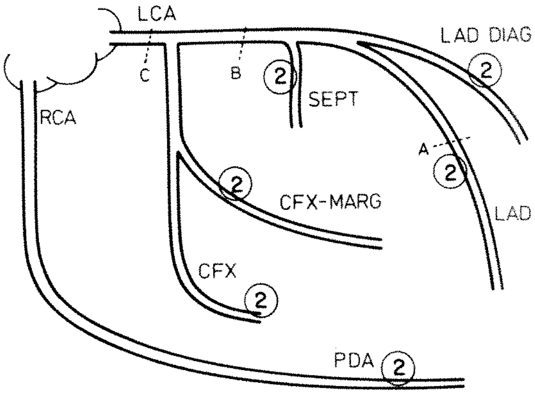

Fig. 1 *The jeopardy score system as a semiquantitative measure of extent of left ventricular involvement by coronary artery disease. The coronary circulation is considered as 6 arterial segments (each of which is designated by the number 2 in the figure). Each segment involved, directly or indirectly (by a lesion proximal to its origin), counts 2 points. For example: patients with single lesions located at points A, B, or C in the figure would have jeopardy scores of 2, 6, and 10, respectively; a patient with 2 lesions, 1 at point A and 1 at point C, would have a jeopardy score of 10. RCA, right coronary artery; LCA, left coronary artery; LAD DIAG, major (largest) diagonal branch of left anterior descending artery; SEPT, major septal perforating artery; LAD, left anterior descending artery beyond the major diagonal and septal branches; CFX-MARG, major marginal branch of the left circumflex artery; CFX, left circumflex artery beyond the major marginal branch; PDA, posterior descending coronary artery.*

Table 1 *Heart rate change and electrocardiographic changes during pacing*

Jeopardy score	*No. of patients*						*Maximum paced heart rate (beats/min)*	
	Total	*Developing angina with pacing*	*Electrocardiographic changes*				*Range*	*Mean*
			*ST depression (V4)**			*Other†*		
			1/2-1 mm	*1-2 mm*	*> 2 mm*			
0 (normal coronary arteries)	5	1	0	0	0	0	95-150	131 ± 11‡
2	9	6	2	1	0	0	120-160	133 ± 6
4	10	8	1	3	0	0	115-150	134 ± 4
6	12	12	1	4	3	4	90-170	125 ± 7
8	11	10	0	5	5	0	90-172	116 ± 8
10	11	10	1	5	2	0	90-150	125 ± 6
12	7	6	1	1	4	1	100-146	122 ± 7

*Horizontally depressed or downsloping ST segments.
†Intraventricular conduction change or ST segment elevation in the area of an old myocardial infarction.
‡In Tables and throughout the text, ± refers to standard error of the mean.

12 (a patient with all 6 segments jeopardised). Significant stenosis was considered as diameter reduction of 50 per cent or more. Significant stenoses are not differentiated from complete occlusions in the jeopardy score system—lesions are counted, or not, on an all-or-none basis. If there was left coronary artery dominance, the 2 points allotted to the posterior descending artery were assigned to the left circumflex artery rather than to the right coronary artery.

Cine left ventriculography was performed in 91 patients. The right anterior oblique ventriculogram was used for purposes of this study. Left ventricular ejection fraction (left ventricular stroke volume/left ventricular end-diastolic volume) was calculated by the modified area-length method as applied to single-plane cine ventriculograms (Kasser and Kennedy, 1969).

STATISTICAL ANALYSIS

Proportions of patient groups with the occurrence of comparable events were analysed by Fisher's exact test or by the χ^2 test. The relation of change in mean systemic arterial pressure to change in cardiac output was examined by linear regression analysis.

Results

In the group of 65 pacing study patients, 5 had angiographically normal coronary arteries (4 without evidence of structural heart disease and 1 with a remote myocardial infarction) and 60 had coronary artery disease (⩾50% diameter reduction) involving at least one coronary artery. Of the latter, 19 had 1-vessel disease, 19 had 2-vessel disease, and 22 had 3-vessel disease; 5 had significant narrowing of the main left coronary artery. All of the spontaneous angina patients had coronary artery disease: 10 had 1-vessel disease, 6 had 2-vessel disease, and 16 had 3-vessel disease. Four spontaneous angina patients had significant narrowing of the main left coronary artery.

HEART RATE AND ELECTROCARDIOGRAPHIC ABNORMALITIES

Of the 60 patients with coronary artery disease who underwent atrial pacing, 52 reported angina during pacing (Table 1). The highest pacing rates achieved are shown in Table 1. Pacing rates did not significantly differ among jeopardy score subgroups. The fraction of patients developing electrocardiographic abnormalities with pacing was related to the angiographic extent of coronary artery disease (Table 1). Electrocardiographic abnormalities occurred in only 7 of 19 patients (37%) with jeopardy scores of 2 or 4, compared with 22 of 23 patients (96%) with jeopardy scores of 6 or 8, and 15 of 18 patients (83%) with jeopardy scores of 10 or 12 ($P < 0·01$).

Heart rate changes associated with chest pain in the 32 patients with spontaneous angina ranged from −15 to +32 beats/min and did not differ among jeopardy score subgroups (mean heart rate change 5, 0, 9, 2, 12, and 8 beats/min in jeopardy score subgroups 2, 4, 6, 8, 10, and 12, respectively). Electrocardiographic abnormalities occurred in 22 of the 24 patients in whom electrocardiograms were recorded during angina, including 7 patients who developed transient ST segment elevations. The latter patients all had significant atherosclerotic coronary disease, by angiographic criteria, in the coronary artery supplying the area of the ventricle corresponding to the site of electrocardiographic abnormality. In the 24 patients who did have an electrocardiogram recorded during angina, the tracing was available for review in only a few; therefore, electrocardiographic descriptions are taken from the daily progress notes in the medical record and data are provided only with regard to whether changes occurred or not.

HAEMODYNAMIC CHANGES

Left ventricular filling pressure at rest did not differ among jeopardy score subgroups: 11 ± 1, 13 ± 2, 12 ± 1, 12 ± 2, 11 ± 2, 10 ± 2 mmHg in jeopardy score subgroups 2, 4, 6, 8, 10, and 12, respectively—pacing study and spontaneous angina patients combined.

The change in left ventricular filling pressure in pacing patients is measured as the difference between the left ventricular filling pressure at baseline and the left ventricular filling pressure at the offset of pacing, so that changes in left ventricular filling pressures produced by ischaemia are more nearly comparable in pacing patients and in patients having spontaneous angina. For purposes of comparison of jeopardy score subgroups, a change in left ventricular filling pressures was judged to be significant if it exceeded an arbitrary threshold value: a rise in the left ventricular end-diastolic pressure of 7 mmHg, chosen because it was the largest change in left ventricular end-diastolic pressure that occurred in patients with angiographically normal coronary arteries, or a rise in pulmonary wedge pressure of 3 mmHg. A change in mean systemic arterial pressure was judged to be significant if it exceeded ±15 mmHg, a value that was chosen because it is the largest change in the mean systemic arterial pressure that occurred in the patients with normal coronary arteries who were paced, as well as being approximately the value of the change in mean systemic arterial pressure in those patients who had a rise in left ventricular filling pressure which separated patients with a rise in cardiac output from those with a fall in cardiac output (see below).

The changes in left ventricular filling pressure and in mean systemic arterial pressure occurring as a consequence of rapid atrial pacing or accompanying spontaneous angina may be summarised by grouping them into 3 patterns. In pattern I, left ventricular filling pressure and mean systemic arterial pressure did not change significantly; in pattern II, left ventricular filling pressure rose, and a rise in the mean systemic arterial pressure (exceeding 15 mmHg) occurred; in pattern III, left ventricular filling pressure rose, but mean systemic arterial pressure did not rise significantly or fall. Only 2 patients who did not have a rise in left ventricular filling pressure had a rise in mean systemic arterial pressure exceeding 15 mmHg; these 2 patients are considered as having a pattern I response. All patients who did not have coronary artery disease exhibited a pattern I response. Ninety-one per cent of patients with a limited extent of coronary artery disease (jeopardy scores of 2 or 4) exhibited pattern I; an approximately equal fraction of patients with jeopardy scores of 6 or 8 developed each of the three patterns; and 78 per cent of patients with the largest extent of coronary artery disease (jeopardy scores of 10 or 12) exhibited pattern III ($P < 0{\cdot}01$) (Fig. 2).

The distribution of patients with regard to the pattern of haemodynamic response within jeopardy score subgroups cannot be explained by differences in the prevalence of propranolol administration or in the prevalence of intra-aortic counterpulsation among the jeopardy score subgroups. Sixty-eight per cent, 69 per cent, and 74 per cent of patients with jeopardy scores of 2 or 4, 6 or 8, and 10 or 12, respectively, were taking propranolol. One patient with a jeopardy score of 2, 1 patient with a jeopardy score of 6, 1 patient with a jeopardy score of 8, 2 patients with a jeopardy score of 10, and 1 patient with a jeopardy score of 12 were undergoing intra-aortic counterpulsation at the time of angina.

The distribution of patients with regard to the pattern of haemodynamic response within jeopardy score subgroups is not influenced by whether ischaemia is spontaneous or pacing-induced or by whether ST segments become elevated or depressed during spontaneous angina (Fig. 3). In addition, patients with main left coronary artery stenosis did not differ from other patients with the same jeopardy

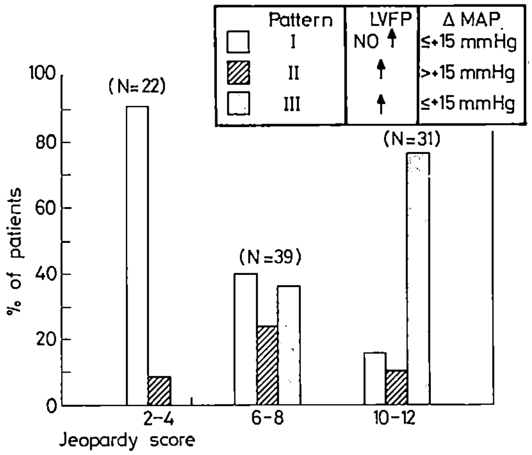

Fig. 2 *The percentage of patients in jeopardy score subgroups 2 and 4, 6 and 8, and 10 and 12 in whom each of the 3 haemodynamic patterns of left ventricular ischaemia developed. Spontaneous angina and pacing study patients are combined. Left ventricular filling pressure (LVFP) ↑ refers to a rise in LVEDP of more than 7 mmHg or a rise in pulmonary wedge pressure of more than 3 mmHg. △MAP, change in mean systemic arterial pressure.*

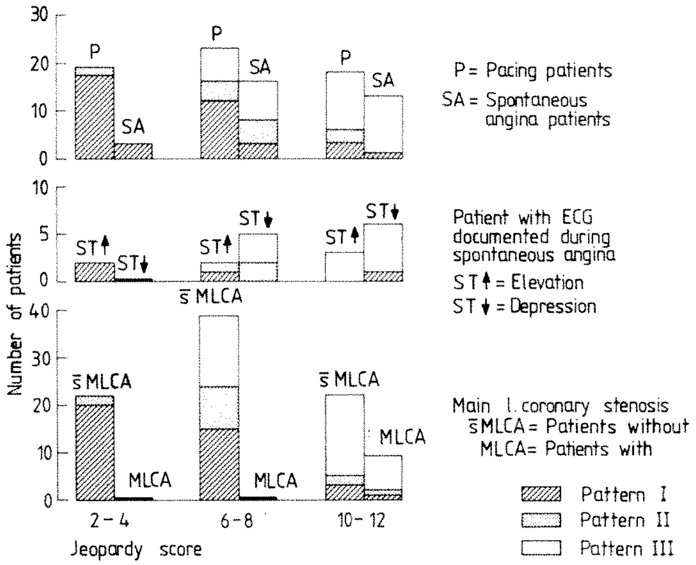

Fig. 3 *The distribution of patients with regard to the haemodynamic response to ischaemia within jeopardy score subgroups. Paced patients are compared with spontaneous angina patients, patients who were documented to have ST segment elevations during spontaneous angina are compared with patients who were documented to have ST segment depressions during spontaneous angina, and patients without main left coronary artery stenosis are compared with patients with main left coronary artery stenosis.*

score with regard to the likelihood that a given haemodynamic response would occur (Fig. 3).

Once the jeopardy score is taken into account, the resting ejection fraction does not appear to exert an independent influence on the pattern of haemodynamic response to ischaemia (Fig. 4).

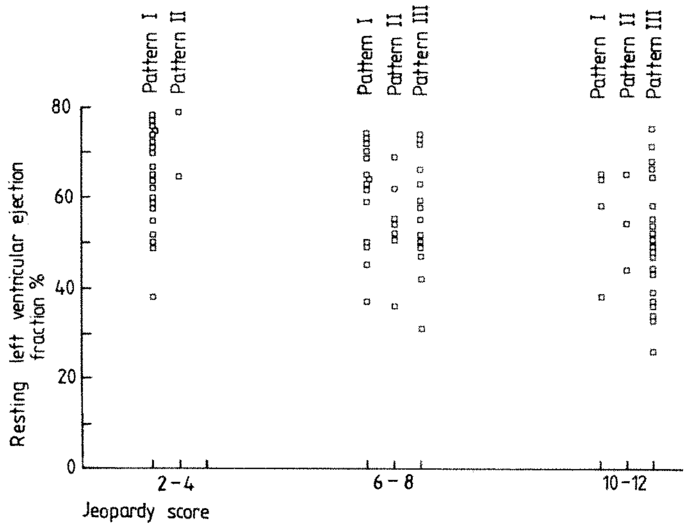

Fig. 4 *The pattern of haemodynamic response during ischaemia according to the patients' resting angiographic left ventricular ejection fraction, and coronary angiographic jeopardy score.*

Table 2 *Pacing study patients: LVFP, stroke work relation**

Jeopardy score	*EF†*	*LVFP change during pacing*	*ΔSV (%)*	*ΔMAP (mmHg)*	*ΔSW (joules)*	*Decline of ventricular function curve‡*	*Pattern of haemodynamic response§*
2	0·71	− 6	−36	+ 6	−0·390	No	I
2	0·71	− 9	−44	+ 2	−0·183	No	I
2	0·73	−10	−33	+ 6	−0·151	No	I
2	0·72	− 8	−35	+ 3	−0·204	No	I
2	0·50	− 5	−47	+ 5	−0·149	No	I
2	0·38	− 9	−49	−10	−0·343	No	I
2	0·65	+ 1	−55	+22	−0·413	Yes	II
4	0·60	− 2	−50	+ 5	−0·724	No	I
4	0·59	− 6	−39	+14	−0·281	No	I
4	0·67	− 8	−44	+12	−0·347	No	I
4	0·64	−11	−41	+ 4	−0·162	No	I
4	0·72	− 9	−29	+ 5	−0·032	No	I
4	0·59	−24	−63	+ 6	−0·170	No	I
4	0·79	+ 8	−39	+18	−0·366	Yes	II
6	0·37	− 4	−13	+13	+0·170	No	I
6	0·63	−11	−58	+ 3	−0·710	No	I
6	0·73	− 9	−54	+ 6	−0·743	No	I
6	0·62	− 6	−53	0	−0·481	No	I
6	0·65	+ 4	−55	+17	−0·213	Yes	I
6	0·59	0	−53	+13	−0·449	Yes	III
6	0·74	−19	−70	− 3	−0·751	No	III
6	0·54	+10	−36	+29	−0·210	Yes	II
6	0·72	+ 5	−36	− 4	−0·551	Yes	III
8	0·72	−11	−60	+ 7	−0·406	No	I
8	0·63	− 2	−20	0	−0·211	No	I
8	0·70	− 4	−37	+15	−0·076	No	I
8	0·59	+ 1	+ 7	+10	+0·131	No	I
8	0·69	−12	−47	+15	−0·531	No	I
8	0·66	+ 5	−35	+15	−0·222	Yes	III
8	0·55	+16	−52	+15	−0·743	Yes	III
8	0·36	+ 7	−24	+22	−0·213	Yes	II
8	0·50	+ 6	−29	+10	−0·331	Yes	I
8	0·62	+ 2	−28	+19	−0·035	Yes	II
8	NA	− 7	−42	+ 5	−0·236	No	III
10	0·38	− 8	−43	+ 5	−0·203	No	I
10	0·44	+ 5	−34	+22	−0·053	Yes	II
10	0·66	+ 3	−35	− 1	−0·221	Yes	III
12	0·64	− 1	−24	+ 9	0	No	I
12	0·65	− 6	−55	+16	−0·265	No	II
12	0·53	+ 7	−46	+15	−0·287	Yes	III
12	0·48	+10	−37	0	−0·235	Yes	III

*The change in left ventricular filling pressure (LVFP), stroke volume (ΔSV), mean arterial pressure (ΔMAP), and stroke work (ΔSW); measurements at the highest paced rate are compared with baseline (unpaced) values. LVFP was recorded as LVEDP in 40 patients and pulmonary wedge pressure in 1 patient.

†EF, left ventricular ejection fraction (measured at rest).

‡See text for definition.

§See text for definition.

NA, not available.

In those patients in whom cardiac output determinations were available (Tables 2 and 3), a decline in the ventricular function curve was demonstrable in only 2 of 24 (8%) with a pattern I response, in 7 of 13 (54%) with a pattern II response, and in 15 of 17 (88%) of those with a pattern III response ($P < 0.01$).

A linear correlation exists between the change in mean systemic arterial pressure and the change in cardiac output for the spontaneous angina patients (Fig. 5A) and for the pacing study patients (Fig. 5B) who had a pattern II or a pattern III response to ischaemia, though the correlation is less close for the paced patients than for the spontaneous angina patients. That the y-intercepts for the best-fit curves shown in Fig. 5A and 5B are 14·8 mmHg and 13·7 mmHg, respectively, rather than zero, suggests that a rise in systemic vascular resistance accompanied left ventricular ischaemia in these patients. In the patients who had a pattern I response to ischaemia (all in whom cardiac output determinations were available were paced patients), the change in mean systemic arterial pressure and the change in cardiac output were unrelated (Fig. 5C).

Discussion

This study shows that the haemodynamic changes occurring in patients with coronary artery disease during rapid atrial pacing or during spontaneous angina may be grouped into three patterns on the

Table 3 *Spontaneous angina: LVFP stroke work relation**

Jeopardy score	*EF*	*ΔSV* (%)	*ΔMAP* (*mmHg*)	*ΔSW* (*joules*)	*ΔLVFP* (*mmHg*)	*Decline of ventricular function curve*†	*Pattern of haemodynamic response*‡
6	0·55	− 9	+45	+0·276	+11	No	II
6	0·52	− 7	+25	+0·125	+ 8	No	II
6	NA	+12	+45	+0·361	+21	No	II
6	0·69	−16	+40	+0·212	+11	No	II
8	0·54	+23	+25	+0·309	+ 6	No	II
8	0·31	+ 4	+ 5	−0·314	+13	Yes	III
8	0·42	−15	+ 5	−0·088	+ 8	Yes	III
10	0·58	−20	+10	−0·391	+11	Yes	III
10	0·44	−14	+15	−0·167	+25	Yes	III
10	0·36	−39	−15	−0·187	+15	Yes	III
12	NA	−36	+10	−0·267	+18	Yes	III
12	0·33	−25	−10	−0·230	+ 4	Yes	III
12	0·71	+ 7	−11	−0·117	+10	Yes	III

*A comparison of haemodynamic measurements that were recorded before and during angina. *ΔSV*, *ΔMAP*, *ΔSW*, and *ΔLVFP* refer to changes in stroke volume, mean arterial pressure, stroke work, and left ventricular filling pressure occurring during angina. Left ventricular filling pressure was recorded as pulmonary wedge pressure in 12 patients and as LVEDP in 1 patient. EF, left ventricular ejection fraction.

†Defined as in text.

‡Defined as in text.

NA, not available.

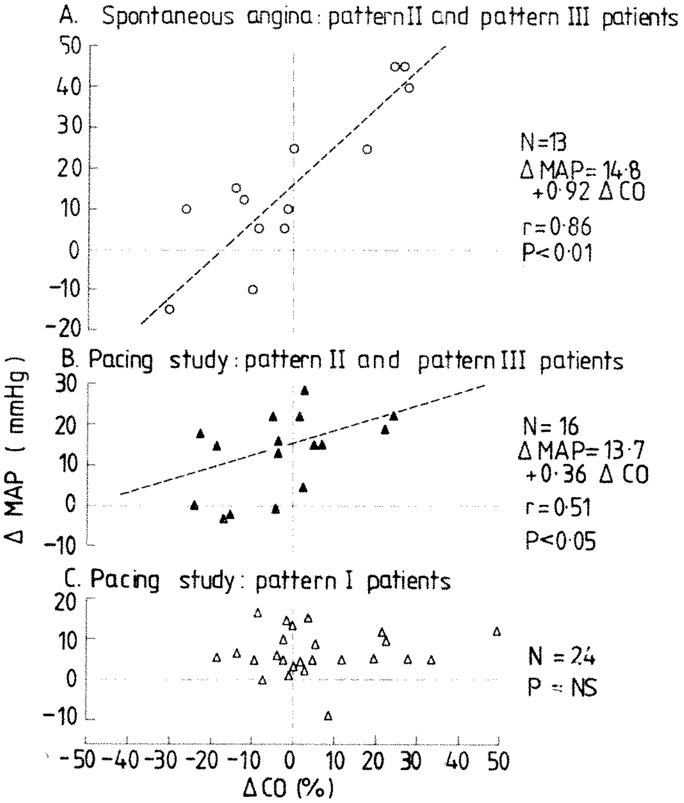

Fig. 5 *Patients with coronary artery disease. The relation of the change in the mean systemic arterial pressure (△MAP) to corresponding changes in cardiac output (△CO) occurring during spontaneous angina or during pacing. (A) Spontaneous angina. All patients (13) in whom cardiac output determinations were available had a pattern II or pattern III response to ischaemia. (B) Pacing study patients with a pattern II or pattern III response. (C) Pacing study patients with a pattern I response.*

basis of the change in left ventricular filling pressure and the change in mean systemic arterial pressure. The likelihood of a patient developing any one of these three patterns is strongly related to the extent of coronary artery disease that is present (Fig. 2)—a finding that suggests that the haemodynamic response to ischaemia is determined by the fraction of left ventricle that becomes dysfunctional during ischaemia. Thus, if the ischaemic fraction is small, a pattern I response occurs; if the ischaemic fraction is intermediate, a pattern II response occurs; and if the ischaemic fraction is large, a pattern III response occurs. Two other observations support such a hypothesis. First, whether ischaemic-induced depression of the ventricular function curve could be demonstrated depended on the pattern of haemodynamic response. Second, within a particular jeopardy score subgroup a given pattern of response could occur in patients with resting left-ventricular ejection fractions that differed over a wide range; therefore, the extent of preischaemic left ventricular dysfunction, in itself, cannot explain the haemodynamic response to ischaemia. The results of the present study do not allow us to say whether the term ischaemic fraction of the left ventricle should refer to the total amount of ventricle that is dysfunctional during ischaemia, that is, the sum of chronically dysfunctional and acutely dysfunctional areas, or only to that portion of the ventricle that has become dysfunctional acutely. It is clear that in some patients at least, namely in those who have a normal resting left ventricular ejection fraction, that the ischaemic fraction is composed totally of areas that have been dysfunctional acutely.

Goldschlager *et al.* (1970), Saltups *et al.* (1971), and Barry *et al.* (1976) also found that the proportion of patients having rises in left ventricular filling pressure during stress (exercise) increased as the extent of coronary artery disease increased, but in the first and second studies a minority of patients had angina, and no ventriculographic data were reported that would allow separation of the effects of acute ischaemia from those of chronic left ventricular functional impairment. Cannom *et al.* (1974) and Roy *et al.* (1975) interpreted the findings of their studies (spontaneous angina and pacing-induced angina, respectively) as showing no relation between the extent of coronary artery disease and haemodynamic changes occurring during ischaemia, but both studies included relatively small numbers of patients.

The results of our study imply that an interaction of a number of factors surrounds an episode of left ventricular ischaemia. The rise in the mean systemic arterial pressure in patients with a pattern II haemodynamic response is, in part, the result of an increase in systemic arteriolar resistance. In addition, venomotor tone may also increase during ischaemia in pattern II patients, causing an increase in venous return, since cardiac output rises (Fig. 5), and, at least in some patients with spontaneous angina, the rise in cardiac output is accompanied by a rise in stroke volume. An alternative explanation for the rise in stroke volume would be an increase in the left ventricular ejection fraction, but that seems unlikely, since the ventricle is ischaemic. Patients in whom the cardiac output falls during ischaemia (pattern III response) (Fig. 5) are almost certainly having an ischaemia-induced decline in left ventricular ejection fraction to account for the rise in left ventricular filling pressure. Angiographic evidence for a fall in ejection fraction in some patients during angina has been provided by Sharma *et al.* (1976). In pattern II patients it remains to be elucidated whether a change in left ventricular compliance (McLaurin *et al.*, 1973; Barry *et al.*, 1974), a change in ejection fraction, or both (Mann *et al.*, 1977) contribute to the rise in left ventricular filling pressure, in addition to a probable increase in venous return.

The results of the present study conflict with the view of Guazzi and co-workers (1975) that haemodynamic alterations in patients with Prinzmetal's variant angina differ from haemodynamic alterations in patients with ST segment depression during angina. When the extent of coronary artery disease is taken into account, the 7 patients in our study with ST segment elevation during spontaneous angina had haemodynamic behaviour that was similar to that of patients with ST segment depression.

Several potential problems in the interpretation of our data warrant discussion. First, rapid atrial pacing data involve measurements that may appear arbitrary. We measured the change in left ventricular filling pressure produced by pacing at the offset of pacing (Khaja *et al.*, 1970) (except for the assessment of a shift in the ventricular function curve—see **Methods**), but we measured the change in mean systemic arterial pressure during pacing, so that the relation between the change in mean systemic arterial pressure and the change in cardiac output could be studied. The value of measuring the change in ventricular filling pressure and the change in mean systemic arterial pressure in this manner is supported by the results. As judged by the relation of the pattern of haemodynamic change to the jeopardy score, ischaemia was equally well detected in pacing patients and in spontaneous angina patients. In addition, the change in mean systemic arterial pressure and the change in the cardiac output were related linearly in both paced and spontaneous angina patients who had a pattern II or pattern III response, which supports the view that a rise in mean systemic arterial pressure during pacing is of physiological significance and not simply an artefact of rapid pacing. That the correlation of the change in mean systemic arterial pressure with the change in cardiac output was closer in patients with spontaneous angina than in those with pacing-induced ischaemia is not surprising. The rapid pacing rates in themselves have some effect on mean systemic arterial pressure (the average change in mean systemic arterial pressure in the 5 control patients was +7 mmHg for example), and a wide range of heart rates is present in the pacing study population.

Second, only a single ischaemic episode per patient was studied. If the degree of ischaemia varied from episode to episode, the apparent relation of the consequences of ischaemia to the angiographic extent of coronary artery disease might thereby be affected. Our interpretation of the data, however, does not depend on the assumption that recurrent episodes of ischaemia in a given patient are identical, but only on the assumption that within an angiographic subpopulation are patients who reveal the range of *possible* degrees of ischaemia for the extent of coronary artery disease that is present.

Third, other factors, not specifically measured in the present study, might affect the haemodynamic consequences of ischaemia or the relation of ischaemia to the coronary arteriogram. For example, haemodynamic manifestations of ischaemia may vary with time during an ischaemic episode in some patients (Guazzi *et al.*, 1975). Mitral regurgitation might develop (Brody and Criley, 1970; Bauman and Sutton, 1975). Many of our patients were on antianginal drugs, and some on intra-aortic counterpulsation—interventions that might affect responses to ischaemia. The jeopardy score does not differentiate total from subtotal coronary artery obstruction, or take collateral vessels into account. And interobserver variability exists in the assessment of the coronary arteriogram (Zir *et al.*, 1976). Nevertheless, though any of these factors might explain differences among individual patients within a jeopardy score subgroup, none of them would affect observed differences between angiographic subpopulations unless they were represented only in some subpopulations and not in others, or unless their occurrence depended on the fraction of left ventricle that was ischaemic. The proportion of patients taking antianginal drugs did not differ among jeopardy score subgroups, and only a few patients had angina while undergoing intra-aortic counterpulsation.

Fourth, in the application of these data to the individual patient, the possible pitfall of over reliance on absolute cutoffs for 'significant' changes should be noted. The threshold values we employed proved useful for investigative purposes, but these were largely arbitrary and might prove misleading for occasional patients who have a 'borderline' change in left ventricular filling pressure, mean systemic arterial pressure, or both. That the use of absolute threshold values for judging significant pressure changes can cause occasional misclassification of the haemodynamic pattern is suggested by our finding that two pattern I patients had a decline in their ventricular function curve during ischaemia, and 2 pattern III patients did not.

Finally, our proposal that the haemodynamic response to ischaemia is determined by the ischaemic fraction of the left ventricle is based primarily upon the distribution of haemodynamic patterns among angiographic subpopulations; hence, it is inferential in nature. Its confirmation will await means whereby the ischaemic fraction of the ventricle can be directly visualised. Whether done by haemodynamic or by other means, however, estimation of the fraction of left ventricle that is ischaemic during angina will almost certainly prove important to our understanding of the natural history of coronary artery disease and whether it is affected by revascularisation procedures or by medical treatment. Such an estimate may also prove important in decisions regarding the urgency of angiographic and surgical procedures for patients having unstable angina in the setting of the coronary care unit.

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QT time in patients treated with alprenolol or placebo after myocardial infarction

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SUMMARY Studies were made on the effects of long-term beta-blockade on the QT interval in patients discharged alive from hospital after myocardial infarction. The patients ($n = 230$) in this study constituted all those who participated in the alprenolol study on postmyocardial patients in Göteborg, Sweden. The study was double-blind (alprenolol 200 mg b.i.d. or placebo) and randomised. The patients were divided into 4 risk groups (1-4) with different predicted mortality. The electrocardiograms before and after 8 weeks of treatment were analysed with respect to heart rate and QT time. There was a decrease in heart rate of about 10 per cent in the alprenolol treated patients. The QT time was not significantly influenced by alprenolol. The rate corrected QT time (QT_c) decreased in the subgroup of the most severely diseased patients (subgroup 4) treated with alprenolol.

In recent years 2 controlled studies have shown that long-term beta-blockade after myocardial infarction reduces the rate of sudden deaths after discharge from hospital (Wilhelmsson *et al.*, 1974; Multicentre International Study, 1975). The specific mechanism of action has not been defined. The most likely explanation for this phenomenon is that lethal arrhythmias are prevented. The relations between the QT time and the duration of the action potential or the fibrillation threshold have been discussed (Schwartz *et al.*, 1976; Raine and Vaughan Williams, 1978). The purpose of the present paper is to analyse the influence of long-term beta-blockade on the QT interval in patients discharged alive from hospital after myocardial infarction.

Table 1 *Criteria for homogeneous risk group allocation of patients with myocardial infarction*

Subgroup no.	*Cardiac damage*	*Criteria*
1	No extensive cardiac damage	
2	Mechanical damage to myocardium	(1) Relative heart-volume: men, $>$ 450 ml/m^2 BSA; women, $>$ 400 ml/m^2 BSA* (2) Alanine transferase $>$ 40 units (Karmen) during first 3 days (3) Body temperature $>$ 38°C during first 3 days (4) Transient atrial flutter and fibrillation
3	Electrical cardiac damage	(1) Ventricular premature beat frequency $>$ 5/min (2) Ventricular tachycardia or ventricular fibrillation (3) AV blocks: (a) PQ $>$ 0·24 s; (b) type II; (c) type III
4	Combined electromechanical damage (subgroups 2 and 3)	

*BSA, body surface area.

Patients and methods

The patients in this investigation constituted all those who participated in the study of alprenolol treatment of patients with acute myocardial infarction after discharge from hospital. All men and women ($n = 230$) in Göteborg, Sweden, with acute myocardial infarction during 1970 to 1971 aged 57 to 67 years with no contraindication to beta-blocking drugs were included. The study was double-blind and started one week after discharge from hospital. The patients were divided into 4 risk groups with differing predicted mortality (Table 1) before random allocation to placebo or active treatment with alprenolol (200 mg b.i.d.; Wilhelmsson *et al.*, 1974; Vedin *et al.*, 1975). Routine examinations took place after every 6-week period. The patients took the tablets at 8 am and 8 pm, and the full dose was given from the beginning of treatment. At each control examination the patients were asked about the intake of tablets. The number of tablets taken was counted at each control examination and the

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urine was assayed for alprenolol content.

Those patients who died, those who had nonfatal reinfarctions, or who developed contraindications against chronic beta-blocking therapy during the first 3 months of follow-up were excluded from this analysis. Predetermined criteria were used for treatment with digitalis and diuretics. No antiarrhythmic drugs were used.

The number of reinfarctions and deaths between 3 months and 2 years after infarction was recorded (Wilhelmsson *et al.*, 1974; Vedin *et al.*, 1975).

Of the 114 patients receiving alprenolol and the 116 patients receiving placebo in the original report (Vedin *et al.*, 1975), 105 on alprenolol and 107 on placebo were analysed (Table 2). For the remainder, one or both of the electrocardiograms needed was missing or the patient had reached an end-point before the second examination. The results will be given for each subgroup (1-4), as well as for all patients together. The numbers of patients in subgroup 3 were too few to be analysed (alprenolol $n = 2$; placebo $n = 3$).

Table 2 *Number of particles in each risk group: patients randomised to treatment (N) and analysed with regard to QT time (n)*

Risk group	*Alprenolol*		*Placebo*	
	N	*n*	*N*	*n*
1	28	26	29	28
2	54	51	57	53
3	4	3	3	3
4	28	25	27	23
Total	114	105	116	107

The electrocardiograms from the day before treatment started (one week after discharge) and the electrocardiogram at the 12-week examination were analysed with respect to RR interval, QT interval, and QT$_c$ (rate-corrected QT interval according to Bazett, 1920). Thus, the patients had been treated for approximately 8 weeks. The resting electrocardiogram was recorded using a 4-channel ink recorder (Elema Schönander 81). The average recording time was 30 seconds at each examination. The values averaged were usually 5 but there were always at least 3 cycles of the strips which had been recorded at 50 mm/s after supine rest for 5 minutes. The electrocardiograms were analysed by one observer (G.N.) without knowledge of the identities of the patients, the treatment given, or the time of the recording. After completion of the analysis the code was broken. Student's t test, paired or unpaired, was used (two-tailed) for statistical analysis. Significant differences were defined for $P < 0{\cdot}05$.

Results

In all the patients on alprenolol, the heart rate fell by 6·4 beats/minute ($P < 0{\cdot}01$). The heart rate was consistently lower at 12 weeks in the alprenolol groups compared with the placebo groups. The difference failed to reach significance in subgroup 1 (Table 3). No consistent changes were observed in

Table 3 *Heart rate, QT interval, and QT$_c$ before and after treatment (mean, standard deviation in brackets)*

Subgroup	*Heart rate beats/min*			*QT interval ms*			*QT$_c$*		
	On drug	*Before drug*	*Change*	*On drug*	*Before drug*	*Change*	*On drug*	*Before drug*	*Change*
1 Alprenolol	69·8 (12·8)	75·1 (12·4)	$-5{\cdot}25^\dagger$ (13·23)	368 (32)	357 (33)	10^* (28)	400 (25)	402 (35)	−2·8 (35)
Placebo	72·1 (14·5)	68·0 (13·5)	$+4{\cdot}15^*$ (12·42)	365 (43)	368 (39)	−3 (33)	403 (33)	396 (30)	7·4 (32)
Significance for difference between drugs	NS	$P \leqslant 0{\cdot}05$	$P \leqslant 0{\cdot}01$	NS	NS	NS	NS	NS	NS
2 Alprenolol	66·5 (12·6)	73·7 (12·8)	$-7{\cdot}14^\ddagger$ (8·6)	366 (36)	357 (36)	8·8 (43)	387 (29)	398 (32)	$-10{\cdot}4^*$ (36)
Placebo	70·2 (14·2)	74·8 (14·2)	$-4{\cdot}65^*$ (20·74)	365 (39)	360 (39)	5·4 (46)	398 (34)	401 (30)	−3·1 (42)
Significance for difference between drugs	NS	NS	NS	NS	NS	NS	$P \leqslant 0{\cdot}10$	NS	NS
4 Alprenolol	68·1 (11·2)	74·1 (14·3)	$-6{\cdot}0^*$ (14·0)	364 (37)	368 (33)	−4·1 (35)	390 (33)	415 (32)	$-25{\cdot}2^\ddagger$ (33)
Placebo	78·8 (15·5)	76·0 (14·7)	+2·8 (11·3)	353 (39)	359 (43)	−6·3 (35)	406 (30)	406 (32)	+0·3 (33)
Significance for difference between drugs	$P \leqslant 0{\cdot}01$	NS	$P \leqslant 0{\cdot}02$	NS	NS	NS	$P \leqslant 0{\cdot}10$	NS	$P \leqslant 0{\cdot}01$

$^*P < 0{\cdot}1$; $^\dagger P < 0{\cdot}05$; $^\ddagger P < 0{\cdot}001$.

the placebo groups though a small increase was noted in subgroup 1.

The uncorrected QT interval is not significantly influenced by any of the treatments in any subgroup (Table 3). After correction for the influence of heart rate a significant shortening of the QT_c was observed in risk group 4 of the alprenolol-treated groups and a non-significant shortening in risk group 2 (Table 3). No changes were seen in the placebo groups or in risk group 1 of the alprenolol group. Generally, before treatment at the start of the trial the QT_c tended to be longer in risk group 4 than in risk groups 1 and 2 and this difference is significant when the results of the alprenolol and placebo groups are analysed together.

The reduction of QT_c in patients with a QT_c above 0·420 (considered normal for a heart rate of 55) was analysed in the alprenolol ($n = 26$) and in the placebo group ($n = 27$). The reduction was particularly pronounced in the alprenolol-treated group (-36 ms vs 23 ms for placebo) and the difference in change between the alprenolol and placebo-treated groups was significant.

Patients with and without concomitant treatment with digitalis were analysed separately in all groups. No significant differences were found between the patients treated with digitalis and those who were not. If anything, digitalis tended to decrease QT_c both alone and especially when used together with alprenolol.

Deaths and reinfarctions were not related to initial QT_c and changes thereof during the remainder of the follow-up time.

Discussion

Previous studies have shown that continued alprenolol treatment has lowered mortality when given to patients with acute myocardial infarction after they have left hospital. The design of the study has been discussed extensively by Wilhelmsson *et al.* (1974) and Vedin *et al.* (1975).

Recently, the QT interval has been studied as a predictor of sudden death in patients with myocardial infarction (Wolf and Schwartz, 1976). Other studies using multivariate techniques have failed to show an independent contribution of the QT time when other variables were considered (Vedin *et al.*, 1977).

Conflicting results are available regarding the influence of chronic beta-blockade on the QT interval. In studies using acute administration of a beta-blocker the QT interval remains unchanged. QT_c, however, is shortened, reflecting the lowering of the heart rate (Stern and Eisenberg, 1969; Seides *et al.*, 1974). Our findings indicate the same effect after chronic administration.

The absence of influence on the QT interval may have several explanations. The patients may not have taken their medication. However, pill counting and urine analysis have shown that more than 80 per cent of the patients took more than 90 per cent of the tablets. The use of other drugs such as digitalis was initially suspected to counteract a further change induced by the beta-blocker. On entry 50 per cent of all patients in the present study were treated with digitalis (Vedin and Wilhelmsson, 1975). In practice concomitant drug usage must be expected. However, propranolol and digoxin have both been shown to lower QT_c. Combining the two drugs led to a further reduction (LeWinter *et al.*, 1977). This observation is supported by our findings. Furthermore, the beta-blockade may influence both the duration of the action potential and the impulse propagation in various regions of the myocardium to produce a constant QT interval.

These findings are in contrast to those of Raine and Vaughan Williams (1976) who found a prolongation of the QT interval in rabbits after beta-blockade. In their work they found that the QT_c began to lengthen after 5 days of treatment, and by 15 days had reached a constant prolongation of 11 per cent, as compared with saline. This change was present after 24 hours when the beta-blocker effect on the heart rate had vanished. Subsequent microelectrode studies on atria and ventricles from the hearts of these rabbits removed after 6 weeks of treatment showed a significant prolongation of action potential duration in the animals receiving active beta-blockade, which parallelled the increase in QT_c. Since such a prolongation is known to be antiarrhythmic the authors propose that this is responsible for the effect seen on survival rate in patients with myocardial infarction. The same authors reported similar findings in a non-randomised study of cardiac patients (Raine and Pickering, 1977) though QT measurements were made with ongoing beta-blocking therapy and not, as in the animal studies, 24 hours after the last dose. The authors suggested that these findings might cause an antiarrhythmic effect of the beta-blockers explaining a mortality reduction in patients treated after myocardial infarction. Differences in study populations could partly explain the differences between those studies and the present one. Focal lesions, for example old myocardial scars in infarction patients, may influence the transmission of the repolarisation vector which can also affect the QT interval regardless of effects on the action potential.

However, the mortality reduction in the post-infarction studies need not be based on a pure antiarrhythmic action of the drug. A beneficial effect of beta-blockers on the balance between regional myocardial demand and supply of oxygen may be important. In pathological states the conditions may indeed vary. For instance, in the so-called long QT syndrome a normalisation of the QT interval has been reported after resection of the left stellate ganglion (Moss and McDonald, 1971; Schwartz *et al.*, 1976). Further clinical improvement together with varying effect on the QT_c is reported after addition of beta-blockers in this condition.

The present findings indicate no effect of long-term beta-blockade on the QT interval in a controlled study, despite a favourable influence on sudden cardiac mortality. The reported change in QT could simply result from the fact that the beta-blocker directly influences the RR interval but it is not clear why this is not seen in all patients. Further studies are needed using a more direct method such as recordings of monophasic action potentials.

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Effects of sodium nitroprusside and phenylephrine on coronary dynamics in patients with normal left ventricular function

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SUMMARY The effects of sodium nitroprusside alone and in combination with phenylephrine were studied at the time of cardiac catheterisation in 10 patients with normal left ventricular function. Nitroprusside was infused to reduce mean arterial pressure in 5 patients with the heart rate free (group 1) and in 5 with the heart rate fixed by atrial pacing (group 2). In group 1 nitroprusside increased heart rate and reduced left ventricular filling pressure and stroke volume. Mean coronary sinus flow increased from 168 ml/min to 187 ml/min, while mean myocardial oxygen extraction fell from 65 to 58 per cent. Mean myocardial oxygen consumption was unchanged. In group 2 nitroprusside reduced left ventricular filling pressure and stroke volume. Mean coronary sinus flow fell from 154 ml/min to 121 ml/min while myocardial oxygen extraction remained unchanged. Mean myocardial oxygen consumption fell from 17 ml/min to 13 ml/min. Phenylephrine restored mean arterial pressure with associated bradycardia in group 1. Left ventricular filling pressure and stroke volume were restored in both groups. In group 1 phenylephrine produced no further changes in mean coronary sinus flow or myocardial oxygen extraction. In group 2 phenylephrine increased mean coronary sinus flow from 121 ml/min to 173 ml/min and increased mean myocardial oxygen consumption from 13 ml/min to 19 ml/min, myocardial oxygen extraction remaining constant. Nitroprusside is a coronary vasodilator but this action may be counteracted by changes in heart rate or afterload.

Sodium nitroprusside has been shown to produce haemodynamic improvement in patients with congestive cardiac failure after acute myocardial infarction (Franciosa *et al.*, 1972; Chatterjee *et al.*, 1973; Parmley *et al.*, 1974). Though there is evidence that this agent reduces experimental myocardial ischaemia (da Luz *et al.*, 1975), a recent clinical and experimental investigation suggested that nitroprusside might increase myocardial ischaemic injury by reducing coronary perfusion pressure or by producing a 'coronary steal' through a dilating action on coronary resistance vessels (Chiariello *et al.*, 1976). Thus, though nitroprusside may be expected to reduce myocardial oxygen consumption by reducing preload and afterload and thereby reduce ischaemic injury in patients with acute myocardial infarction, it may have the reverse effect if it produces coronary vasodilatation.

This study was performed in an attempt to define the effects of nitroprusside on coronary dynamics under varying haemodynamic conditions.

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Patients and methods

Ten patients with suspected coronary artery disease were studied at the time of cardiac catheterisation. Informed consent was obtained in all cases. All patients had stable angina pectoris as their presenting symptom. There were 9 men and 1 woman aged between 39 and 63 years (Table 1).

Coronary arteriography and left ventriculography were performed from the femoral artery using the Seldinger technique.

Following the diagnostic procedure a No. 7 Desilets-Hoffman cannula was placed in the femoral artery for systemic arterial pressure measurement and arterial blood sampling. A Cournand catheter was advanced to the pulmonary artery from the femoral vein. A Ganz coronary sinus thermodilution catheter was advanced to the coronary sinus from a left antecubital vein. Lead II of the electrocardiogram was recorded. Systemic, pulmonary artery, and coronary sinus pressures were measured using Bell and Howell transducers, and were recorded by a Mingograf 82 recorder.

Table 1 *Coronary arteriographic findings*

Case no.	*Age and sex*	*Coronary arteriogram*
Group 1		
1	39F	Normal
2	54M	Normal
3	61M	3-vessel disease
4	63M	3-vessel disease
5	61M	2-vessel disease
Group 2		
6	48M	3-vessel disease
7	48M	2-vessel disease
8	58M	3-vessel disease
9	60M	3-vessel disease
10	53M	1-vessel disease

Group 1—heart rate free.
Group 2—heart rate fixed.

Coronary sinus flow, which has been shown to represent nearly all of the left ventricular myocardial blood flow (Hood, 1968), was determined using the continuous thermodilution technique of Ganz *et al.* (1971). These authors showed close agreement between this and other methods of measuring myocardial blood flow (Ganz *et al.*, 1971). In an attempt to include the contribution to coronary sinus flow of the posterior interventricular vein, close approximation of the downstream thermistor to the orifice of the coronary sinus was ensured by injection of contrast medium before each flow estimation.

Arterial and coronary sinus oxygen contents were measured by the fuel-cell technique (Lex O_2 Con) which has been found to give results in close agreement with those obtained using the manometric technique of Van Slyke (Adams and Cole, 1975).

Cardiac output was measured by the indocyanine green dye dilution technique, the dye being injected into the pulmonary artery and sampled from the femoral artery.

After at least 40 minutes had elapsed from the time of injection of contrast medium, control recordings of heart rate, systemic and pulmonary arterial pressures, and coronary sinus pressure were made together with determinations of cardiac output and coronary sinus flow.

Simultaneous arterial and coronary sinus blood samples were withdrawn for oxygen content estimations. A solution of sodium nitroprusside (100 μg/ml 5% dextrose) was infused using an IVAC controlled infusion pump until a fall in mean systemic arterial pressure of between 5 and 15 mmHg was achieved. Measurements were then repeated. Phenylephrine (4 μg/ml 5% dextrose) was then infused using a Harvard pump at a rate sufficient to raise mean arterial pressure as closely as possible to control level.

To eliminate the effects of changes in heart rate a group of 5 patients whose heart rate was fixed by atrial pacing at 20 beats/minute above the sinus rate was studied (group 2). The results from this group were compared with those from 5 patients in sinus rhythm (group 1). The patients in each group were randomly selected.

CALCULATIONS

Mean systemic arterial pressure (MAP), mean pulmonary arterial pressure (MPA), and mean coronary sinus pressure (MCSP = mean right atrial pressure) were obtained by electronic integration of the phasic pressures. Pulmonary artery end-diastolic pressure (PADP) was taken to represent left ventricular filling pressure (Bouchard *et al.*, 1971).

Cardiac index (CI) (l/min per m^2) = cardiac output (CO)/body surface area.

Stroke volume index (ml per m^2) = stroke volume/body surface area.

Systemic vascular resistance (dynes s cm^{-5}) = 80 × (MAP − MCSP)/CO.

Pulmonary vascular resistance (dynes s cm^{-5}) = 80 × (MPA − PADP)/CO.

Coronary vascular resistance (dynes s cm^{-5}) = 80 000 × (MAP − MCSP)/CSF where CSF = coronary sinus flow (ml/min).

Myocardial oxygen consumption (ml/min) = CSF × AV O_2 difference where AV O_2 difference (ml/100 ml) = coronary arteriovenous oxygen difference.

Myocardial oxygen extraction (%) = 100 × AV O_2 difference/arterial O_2 content.

Left ventricular stroke work index (g m per m^2) = (MAP − PADP) × SVI × 0·0136.

Statistical analysis was by the paired Student's t test.

Results

CINEANGIOCARDIOGRAPHIC FINDINGS

Left ventricular ejection fraction was normal in all patients. Coronary arteriography demonstrated greater than 50 per cent stenosis of one or more of the major coronary arterial branches in eight patients. In two patients the coronary arteries were normal (Table 1).

EFFECTS ON SYSTEMIC HAEMODYNAMICS (Table 2)

Group 1

The mean fall in mean arterial pressure after nitroprusside infusion was 9 mmHg. There was an associated rise in heart rate in all patients (mean 23 beats/minute). A fall in left ventricular filling

Table 2 *Systemic haemodynamic effects of nitroprusside and phenylephrine*

Case no.	*HR (beats/min)*			*MAP (mmHg)*			*CI (l/min per m²)*			*SVI (ml per m²)*			*PADP (mmHg)*			*LVSWI (g m per m²)*			*SVR (dynes s cm⁻⁵)*			*PVR (dynes s cm⁻⁵)*		
	C	*N*	*N+P*	*C*	*N*	*N+P*	*C*	*N*	*N+P*	*C*	*N*	*N+P*	*C*	*N*	*N+P*	*C*	*N*	*N+P*	*C*	*N*	*N+P*	*C*	*N*	*N+P*
Group 1																								
1	100	150	88	88	73	85	5·5	4·2	4·8	55	28	55	12	8	10	57	25	56	840	923	926	20	52	23
2	70	80	72	108	92	110	4·1	3·8	3·8	58	48	53	12	10	14	76	54	69	1171	1090	1285	45	24	24
3	88	105	57	90	85	98	3·8	2·9	2·9	44	28	51	10	8	12	48	29	55	1003	1243	1462	22	29	89
4	75	95	60	86	80	100	4·1	3·8	—	55	38	—	12	8	18	56	37	—	790	856	—	30	45	—
5	60	80	53	94	92	100	2·3	1·9	2·5	39	24	48	12	8	10	43	27	55	1437	1760	1358	33	80	91
Mean	79	102	66	93	84	99	4·0	3·3	3·5	50	33	52	12	8	13	56	34	59	1048	1174	1258	30	46	57
± SEM	7·0	12·9	6·3	3·9	3·6	4·0	0·5	0·4	0·5	3·7	4·4	1·5	0·4	0·4	1·5	5·6	5·3	3·4	118	161	116	4·5	9·9	19·2
P		< 0·05	< 0·02		< 0·05	< 0·005		< 0·025	NS		< 0·005	< 0·02		< 0·005	< 0·05		< 0·001	< 0·001		NS	NS		NS	NS
Group 2																								
6	95	95	95	90	84	98	5·6	4·8	4·8	59	50	50	11	8	10	63	52	60	611	676	783	14	16	16
7	110	110	110	90	85	94	5·4	4·3	4·9	49	39	45	10	6	16	53	42	48	726	861	836	16	20	36
8	90	90	90	86	70	105	2·6	2·1	3·1	29	23	35	8	6	10	30	20	45	1527	1577	1584	73	45	45
9	90	90	90	102	90	110	2·4	2·2	2·4	27	24	27	16	12	16	32	25	34	1745	1723	1890	73	61	73
10	85	85	85	92	76	96	2·9	2·4	2·6	34	28	31	12	10	12	37	25	35	1283	1309	1502	60	36	49
Mean	94	94	94	92	81	101	3·8	3·2	3·6	40	33	38	11	8	13	43	33	44	1178	1229	1319	47	40	44
± SEM	4·3	4·3	4·3	2·7	3·5	3·0	0·7	0·6	0·5	6·2	5·1	4·3	1·3	1·2	1·4	6·4	6·0	4·8	221	202	218	13·3	7·3	9·3
P					< 0·01	< 0·01		< 0·01	NS		< 0·005	NS		< 0·005	< 0·05		< 0·001	< 0·02		NS	NS		NS	NS

HR, heart rate; MAP, mean arterial pressure; CI, cardiac index; SVI, stroke volume index; PADP, pulmonary artery end-diastolic pressure; LVSWI, left ventricular stroke work index; SVR, systemic vascular resistance; PVR, pulmonary vascular resistance; SEM, standard error of mean; C, control; N, nitroprusside; N + P, nitroprusside + phenylephrine; P, significance (significance for N + P refers to change from N).

pressure (mean 4 mmHg) was accompanied by significant falls in cardiac index (mean 0·7 l/min per m²), stroke volume index (mean 17 ml per m²), and left ventricular stroke work index (mean 22 g m per m²). There was a variable effect on systemic and pulmonary vascular resistance with no significant change in mean values.

The restoration of mean arterial pressure by phenylephrine was associated with falls in heart rate to or below control levels (Fig. 1). In 3 patients there was a bradycardia of 60 beats/minute or below after phenylephrine infusion. Left ventricular filling pressure, stroke volume index, and left ventricular stroke work index were restored to control levels. Cardiac index was not fully restored in 3 of the 4 patients in whom technically satisfactory cardiac outputs were obtained, reflecting a failure of stroke volume to increase sufficiently to compensate for the relative bradycardia.

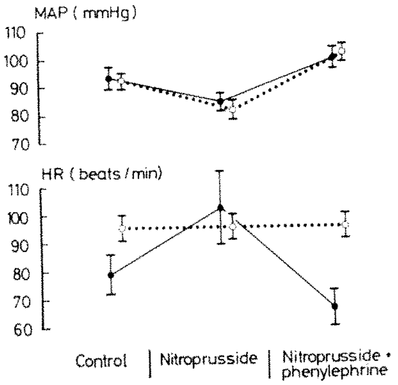

Fig. 1 *Effect of nitroprusside and nitroprusside plus phenylephrine on mean arterial pressure (MAP) and heart rate (HR). Closed circles, continuous line—heart rate free; open circles, broken line—heart rate fixed.*

Group 2

Nitroprusside produced a mean fall in mean arterial pressure of 11 mmHg. Left ventricular filling pressure fell (mean 3 mmHg) together with cardiac index (mean 0·6 l/min per m²) and left ventricular stroke work index (10 g m per m²). Stroke volume index fell (mean 7 ml per m²), though to a lesser degree than in group 1 in the absence of tachycardia.

Changes in mean systemic and pulmonary vascular resistance were not significant.

There was a tendency for phenylephrine to reverse the haemodynamic changes induced by nitroprusside.

Changes in mean values for cardiac index, stroke volume index, pulmonary arterial end-diastolic pressure, and left ventricular stroke work index for the two groups are illustrated in Fig. 2.

EFFECTS ON CORONARY DYNAMICS (Table 3)

Group 1

Nitroprusside increased coronary sinus flow in all patients (mean 19 ml/min). This was associated with highly significant falls in mean coronary AV O_2 difference and myocardial oxygen extraction. There was no significant change in mean myocardial

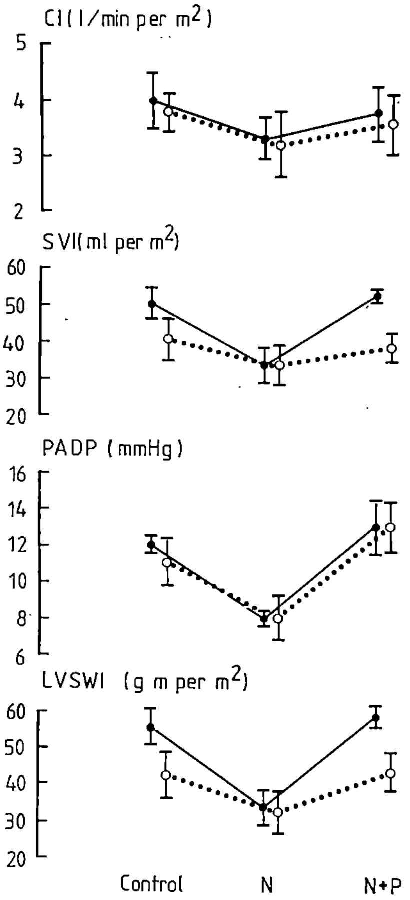

Fig. 2 *Effect of nitroprusside and nitroprusside plus phenylephrine on cardiac index (CI), stroke volume index (SVI), pulmonary artery end-diastolic pressure (PADP), and left ventricular stroke work index (LVSWI). Closed circles, continuous line—heart rate free; open circles, broken line—heart rate fixed. N = nitroprusside, N+P = nitroprusside plus phenylephrine.*

oxygen consumption. Mean coronary vascular resistance fell significantly.

Phenylephrine further increased coronary sinus flow in 3 patients. Slight reductions in flow occurred in 2. However, in 4 patients the reduction in coronary AV O_2 difference and myocardial oxygen extraction was maintained or increased (Fig. 3). There was no significant change in mean myocardial oxygen consumption during phenylephrine infusion. There were variable individual changes in coronary vascular resistance with no change in the mean.

Group 2

In contrast to group 1, nitroprusside consistently produced falls in coronary sinus flow with no significant changes in coronary AV O_2 difference or myocardial oxygen extraction. Hence there was a uniform fall in myocardial oxygen consumption. Mean coronary vascular resistance increased significantly.

The effects of phenylephrine differed from those found in group 1. There was a uniform rise in coronary sinus flow which was not accompanied by significant changes in coronary AV O_2 differences or myocardial oxygen extraction in 4 patients, though there was a fall in the latter in one (Fig. 3). Myocardial oxygen consumption increased in all patients. Changes in myocardial oxygen consumption for individual patients are compared with group 1 in Fig. 4. Coronary vascular resistance fell in 4 patients and increased in 1.

Discussion

In this study where nitroprusside was given to patients with normal left ventricular function there were falls in left ventricular filling pressure and systemic arterial pressure resulting in falls in cardiac output and left ventricular stroke work. In patients in sinus rhythm there was a conspicuous reflex tachycardia. These changes contrast with those observed in patients with left ventricular failure where cardiac index and left ventricular stroke work improve (Chatterjee *et al.*, 1973).

In patients in group 1, these haemodynamic changes produced no significant change in myocardial oxygen consumption, suggesting that changes in its determinants occurred in such a way that their influences on this variable counteracted each other. Under the circumstances nitroprusside increased coronary sinus flow, and reduced coronary vascular resistance and myocardial oxygen extraction.

In contrast, in group 2 where changes in heart rate were artificially eliminated by atrial pacing nitroprusside decreased myocardial oxygen consumption.[1] The decrease in myocardial oxygen

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[1] The control mean value for myocardial oxygen consumption in this group was slightly lower than that of group 1 (Table 3). This is unexpected since the higher heart rate in group 2 should have given a higher value for myocardial oxygen consumption. A possible explanation is that the low values for coronary sinus flow obtained for 2 patients in this group (cases 7 and 8) represented great cardiac vein flow if the posterior interventricular vein joined the coronary sinus nearer its orifice than usual so that the proximal thermistor of the catheter was situated upstream to the posterior interventricular vein. The values for myocardial oxygen consumption in these patients would, therefore, represent a smaller fraction of total myocardial oxygen consumption than in the remaining patients in this group. It is, however, reasonable to assume that changes in this fraction were representative of changes in total myocardial oxygen consumption.

Table 3 *Coronary haemodynamic effects of nitroprusside and phenylephrine*

	CSF (*ml/min*)			*AV O_2 diff.* (*ml/100 ml*)			*O_2 extr* (%)			*$M\dot{V}O_2$* (*ml/min*)			*CVR* (*dynes s cm^{-5} × 10^{-3}*)		
	C	*N*	*N+P*	*C*	*N*	*N+P*	*C*	*N*	*N+P*	*C*	*N*	*N+P*	*C*	*N*	*N+P*
Group 1															
1	136	146	150	12·0	10·5	10·9	66	58	60	16	15	16	49	39	43
2	277	295	273	13·3	10·8	11·4	63	53	54	37	32	31	30	24	31
3	142	181	228	11·5	10·1	9·5	62	54	51	16	18	22	50	38	34
4	150	173	150	12·5	11·4	12·8	67	61	68	19	20	19	43	35	51
5	137	138	178	13·3	12·4	12·5	68	64	64	18	17	22	51	51	51
Mean	168	187	196	12·5	11·0	11·4	65	58	59	21	20	22	45	37	42
± SEM	27	28	24	0·4	0·4	0·6	1·2	2·0	3·1	4·0	3·0	2·5	4·0	4·3	4·1
P		< 0·05	NS		< 0·01	NS		< 0·001	NS		NS	NS		< 0·05	NS
Group 2															
6	273	230	292	10·9	10·7	10·9	59	58	58	30	25	32	25	29	26
7	85	73	121	12·5	12·5	11·2	63	61	55	11	9	14	83	92	61
8	84	63	88	13·8	14·5	14·7	71	75	76	12	9	13	80	87	94
9	107	96	104	11·2	10·8	11·0	61	59	60	12	10	11	72	72	64
10	220	143	262	8·7	9·7	9·3	41	45	44	19	14	24	31	40	28
Mean	154	121	173	11·4	11·6	11·4	59	60	59	17	13	19	58	64	55
± SEM	39	30	43	0·8	0·8	0·9	5·0	4·8	5·1	3·6	3·0	4·0	12·5	12·6	12·7
P		NS	< 0·05		NS	NS		NS	NS		< 0·01	< 0·05		< 0·05	NS

CSF, coronary sinus flow; AV O_2 diff., coronary arteriovenous oxygen content difference; O_2 extr, myocardial oxygen extraction; $M\dot{V}O_2$, myocardial oxygen consumption; CVR, coronary vascular resistance; SEM, standard error of mean; C, control; N, nitroprusside; N + P, nitroprusside + phenylephrine; P, significance (significance for N + P refers to change from N).

consumption in group 2 was accompanied by a fall in coronary sinus flow, and an increase in coronary vascular resistance with no change in myocardial oxygen extraction.

While the systemic haemodynamic effects of phenyleprhine were similar in the two groups, there were differences in its effects on coronary dynamics. In group 1 where there was a fall in heart rate,

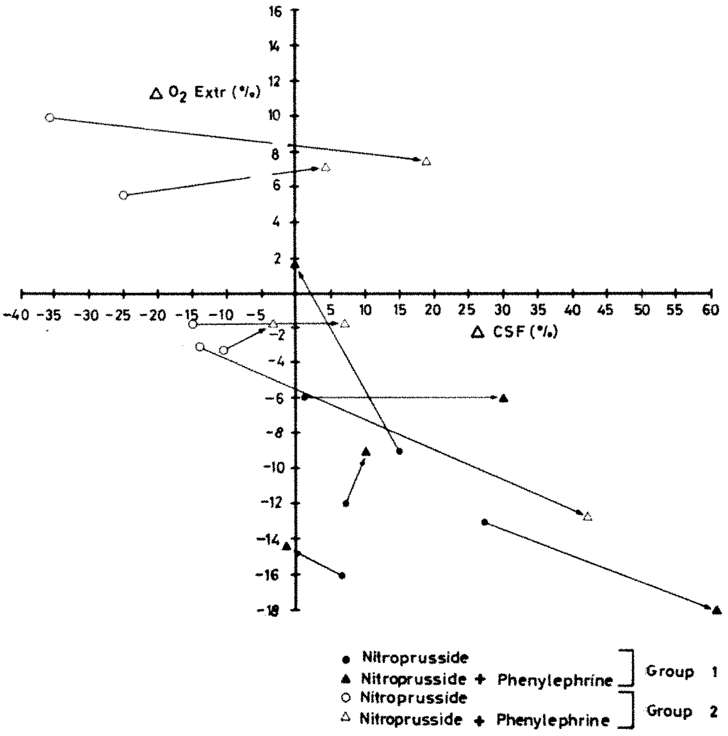

Fig. 3 *Effect of nitroprusside and nitroprusside plus phenylephrine on percentage change in myocardial oxygen extraction* (*ΔO_2 extr*) *and coronary sinus flow* (*ΔCSF*). *Group 1—heart rate free, group 2—heart rate fixed.*

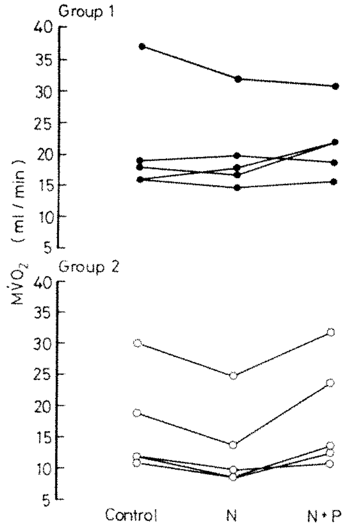

Fig. 4 *Effect of nitroprusside and nitroprusside plus phenylephrine on myocardial oxygen consumption* ($M\dot{V}O_2$) *for individual patients.* N = *nitroprusside,* $N+P$ = *nitroprusside plus phenylephrine.*

myocardial oxygen consumption was unchanged. The increased perfusion pressure under these circumstances resulted in variable changes in coronary sinus flow, though the decreased myocardial oxygen extraction was in general maintained (Fig. 3). In group 2 the increase in systemic arterial pressure by phenylephrine was associated with an increase in myocardial oxygen consumption. Coronary sinus flow increased while myocardial oxygen extraction remained unchanged. Coronary vascular resistance fell in 4 patients.

The interpretation of these observations is complex but it appears that the net effect of nitroprusside on coronary dynamics, at least in patients with normal left ventricular function, depends critically upon prevailing changes in myocardial oxygen consumption. A hypothesis explaining the data may be constructed from evidence obtained from previous studies concerning the control of myocardial blood flow.

In the experimental animal changes in myocardial oxygen demand are met by changes in myocardial blood flow, myocardial oxygen extraction remaining constant (Katz and Feinberg, 1958). That this is true in man is supported by a recent study from this laboratory where changes in myocardial blood flow induced by beta-adrenergic blockade and rapid atrial pacing were associated with a constant myocardial oxygen extraction (Stephens *et al.*, 1978). The relation between myocardial blood flow (oxygen supply) and oxygen demand is maintained primarily by autoregulation, that is a tissue oxygen tension sensitive system involving the release of local metabolites which act to produce changes in coronary vascular tone (Berne, 1964).

This relation may be modified by a vasodilator drug such as nitroprusside which may reduce myocardial oxygen supply relative to demand by reducing coronary perfusion pressure (systemic arterial pressure). Conversely, the myocardial oxygen supply/demand relation may be improved by coronary vasodilatation resulting from a direct action of the drug on the coronary resistance bed. If the latter effect dominated, an improved supply/demand relation would be manifest as an increase in myocardial blood flow, a decrease in myocardial oxygen extraction, or both. Since, however, autoregulation provides a potential coronary vasoconstrictor mechanism, the coronary vasodilator effect of nitroprusside may be prevented if a fall in myocardial oxygen demand initiates a powerful autoregulatory vasoconstrictor response. Similarly, the coronary effects of phenylephrine may not be confined to the increase in coronary perfusion pressure but may encompass complex interactions between changes in myocardial oxygen demand and autoregulation, and the direct effects of nitroprusside and phenylephrine on the coronary arterial vessels.

In the present study it is possible to speculate that in group 1 the effect of the rise in heart rate on myocardial oxygen consumption was balanced by a fall in left ventricular afterload and thus wall tension (Sarnoff *et al.*, 1958; Graham *et al.*, 1968). Under these circumstances there was a primary coronary vasodilator effect of nitroprusside when autoregulation was not initiated. However, in group 2 where there was a fall in myocardial oxygen consumption, autoregulation produced coronary vasoconstriction sufficient to prevent nitroprusside-induced coronary vasodilatation.

These considerations may be extended to provide a possible explanation of the observed effects of the phenylephrine. In group 1 the fall in heart rate balanced the effect of increased afterload on myocardial oxygen consumption so that autoregulation was not initiated. Hence, the coronary vasodilator action of nitroprusside was maintained, though myocardial blood flow was not substantially augmented by the increased coronary perfusion pressure, perhaps because of an opposing coronary vasoconstrictor effect of phenylephrine. In group 2 the net effect of phenylephrine was to produce an increase in myocardial oxygen consumption. Coronary vasodilatation occurred as a result of autoregulation but nitroprusside did not augment this response as shown by the failure of myocardial oxygen extraction to fall. This may have been because of an opposing vasoconstrictor action of phenylephrine or more powerful autoregulatory vasodilatation masking that of nitroprusside.

An important assumption in this study is that the presence or absence of coronary artery disease was unimportant with regard to the observed changes in coronary dynamics. Experience in this laboratory has shown that coronary sinus flow accurately represents changes in myocardial blood flow over a wide range of flows in patients with and without coronary artery disease (Stephens *et al.*, 1978). Further, coronary sinus flow increases in an identical linear fashion with incremental increases in heart rate in patients with and without coronary artery disease up to the point of development of angina (Yoshida *et al.*, 1971). It is unlikely, therefore, that the presence of coronary arterial narrowing in the patients in this study influenced the observed changes in myocardial blood flow.

This study provides evidence for a coronary vasodilator effect of nitroprusside in man. However, this action may be prevented by artificially abolishing the associated tachycardia and so reducing myocardial oxygen consumption. The correction of nitroprusside-induced hypotension by phenylephrine does not significantly improve global myocardial oxygenation and may under certain circumstances increase myocardial oxygen consumption.

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Pulmonary hypertension and sudden death in aortic stenosis[1]

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SUMMARY Sudden death is now an infrequent occurrence in severe aortic stenosis. However, an impressive increase in pulmonary arteriolar resistance has been found in some patients with end-stage aortic stenosis dying suddenly or deteriorating suddenly after catheterisation. Pulmonary hypertension does not seem to cause sudden death, but, in conjunction with decreased cardiac output, a critical reduction in aortic orifice area, and left ventricular failure, pulmonary hypertension identifies a population at significant risk. The rare finding of severe pulmonary hypertension in aortic stenosis should be considered an important marker for sudden death and in association with left ventricular failure may indicate an urgent need for valve replacement, regardless of the apparent clinical condition of the patient. In a small number of subjects catheterised postoperatively, increased pulmonary arteriolar resistance lessened rapidly.

Sudden death in patients with severe aortic stenosis is a well-recognised event which was estimated in older reports to occur in 5 to 15 per cent of patients (Mitchell *et al.*, 1954; Takeda *et al.*, 1963; Friedberg, 1966; Campbell, 1968). With present clinical recognition and diagnostic catheterisation, patients are usually referred earlier for aortic valve replacement, and sudden death is rare.

Within 24 hours of cardiac catheterisation, 4 patients with critical aortic stenosis died suddenly with heart failure and cardiogenic shock. In all, pronounced left ventricular failure and severe pulmonary hypertension with increased pulmonary arteriolar resistance were found. Three others deteriorated suddenly after study and underwent successful emergency aortic valve replacement. Review of the haemodynamics in 3 other patients with critical aortic stenosis who died suddenly while awaiting elective valve replacement indicated a similar pattern. With this knowledge 5 additional subjects identified by similar haemodynamics after catheterisation were subjected to immediate aortic valve replacement, with survival. The Smeloff-Cutter aortic prosthesis was used in all operated patients. These 15 patients are termed the subject group. Clinical and haemodynamic data concerning the subject group are listed in Tables 1 and 2.

Methods and subjects

In order to investigate this problem, the records of 72 patients with critical aortic stenosis identified over a 5-year period were reviewed.

Haemodynamic data were determined in standard fashion by right heart catheterisation and by measurement of transaortic gradients by transseptal left ventricular catheterisation and central aortic catheterisation. Contrast injections were limited to the coronaries and aortic root alone because of the risk of transseptal left ventricular angiography (Braunwald *et al.*, 1964). Consequently, left ventricular injections for assessment of mitral regurgitation were not performed. Patients with more than minor angiographic evidence of aortic regurgitation were excluded. The clinical deterioration of patients after catheterisation could not be related to arrhythmias, the trauma of a prolonged procedure, or acute myocardial infarction.

Statistical analysis was applied using a negative t test to identify whether within the population separate subsets of individuals were present. Frequency histograms and distribution curves of the

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Table 1 *Sudden death in aortic stenosis: clinical and haemodynamic findings*

Case no.	*Age (y)*	*LA*	*PA*	*Ao*	*LV*	*CI*	*AVA*	*PAR*	*Coronaries*	*Comment*
1	59	$\overline{20}$*	78/30 ($\overline{51}$)	78/45	190/23	1·4	0·24	992	Normal	Died of cardiogenic shock 3 h after study awaiting operation
2	57	$\overline{35}$	113/50 ($\overline{70}$)	106/60	273/41	1·1	0·13	1528	Normal	Died in lift 48 h after study on way to operation
3	49	$\overline{20}$	73/27 ($\overline{44}$)	110/52	264/26	3·2	0·41	304	Ostial right coronary artery block	Died suddenly 6 weeks after study awaiting operation
4	61	$\overline{15}$	42/20 ($\overline{31}$)	120/67	222/21	2·4	0·50	280	60% mid-right coronary artery block	Died suddenly 1 mth after study awaiting operation
5	60	$\overline{17}$	56/31 ($\overline{48}$)	135/80	204/28	1·6	0·28	864	80% prox. left anterior descending coronary artery block	Died 2 h after study on way to operation
6	49	$\overline{20}$*	45/24 ($\overline{30}$)	115/50	220/25	2·1	0·28	221	Not done	Died in ante-room awaiting operation
7	54	$\overline{31}$	70/35 ($\overline{52}$)	98/65	295/36	2·0	0·20	437	Not done	Died suddenly 4 h after study

*PA wedge pressure.

LA, left atrial mean; PA, pulmonary artery; Ao, aortic pressure; LV, left ventricle; CI, cardiac index (l/m^2); AVA, aortic valve area; PAR, pulmonary arteriolar resistance (dynes cm s^{-5}).

entire population were generated by a computer and compared with those patients dying or suddenly deteriorating (Fig.).

Results

The haemodynamic profile of the 72 patients is presented in Table 3. The normal value for the cardiac index was greater than 2·7 l/m^2, the value for left ventricular filling pressure was 14 mmHg or less, and for the critical reduction in aortic valve area it was assumed to be 0·5 cm^2 or less (Gorlin *et al.*, 1955). The normal value for pulmonary arteriolar resistance was less than 160 dynes cm s^{-5}. As expected, in those dying suddenly or deteriorating after study, mean cardiac index and valve area were significantly reduced and left heart filling pressure was high. Though mean pulmonary artery pressure and resistance were somewhat raised for the entire population, in subjects dying suddenly or needing

Table 2 *Aortic stenosis with pulmonary hypertension: clinical and haemodynamic findings in 8 patients who underwent emergency valve surgery*

Case no.	*Age (y)*	*LA*	*PA*	*Ao*	*LV*	*CI*	*AVA*	*PAR*	*Coronaries*	*Comment*
8	56	$\overline{17}$	100/51 ($\overline{72}$)	98/72	205/22	3·1	0·52	648	Normal	Severe congestive heart failure before surgery; died of myocarditis 4 mth after aortic valve replacement
9	63	$\overline{33}$	67/33 ($\overline{49}$)	143/100	225/38	2·4	0·40	376	Normal	Severe congestive heart failure; IHSS on postop. cath.
10	61	$\overline{17}$	42/19 ($\overline{30}$)	80/53	171/24	1·3	0·18	482	Not done	Cardiogenic shock preop.; acute myocardiac infarct 18 mth postop.
11	51	$\overline{31}$	65/30 ($\overline{44}$)	90/64	160/40	1·5	0·30	484	Not done	Shock after study; minor congestive heart failure postop.
12	60	$\overline{28}$	90/35 ($\overline{49}$)	110/68	208/32	3·1	0·53	226	Not done	Severe congestive heart failure preop.; died 5 y postop. of cerebral haemorrhage
13	57	$\overline{35}$	112/57 ($\overline{68}$)	87/61	190/32	2·3	0·33	587	Normal	Severe congestive heart failure preop.; minor congestive heart failure postop.
14	60	$\overline{31}$	72/32 ($\overline{46}$)	86/68	145/25	0·98	0·15	769	Normal	Diagnosis unsuspected until study; now asymptomatic
15	67	$\overline{23}$	97/47 ($\overline{65}$)	92/64	141/27	1·6	0·44	1159	Complete obstruction of left anterior descending coronary artery and right coronary artery	Valve replacement, double coronary bypass and left ventricular aneurysm resection

LA, left atrial mean; PA, pulmonary artery; Ao, aortic pressure; LV, left ventricle; CI, cardiac index; AVA, aortic valve area; PAR, pulmonary arteriolar resistance (dynes cm s^{-5}); AVR, aortic valve replacement; IHSS, idiopathic hypertrophic subaortic stenosis; AMI, acute myocardial infarct.

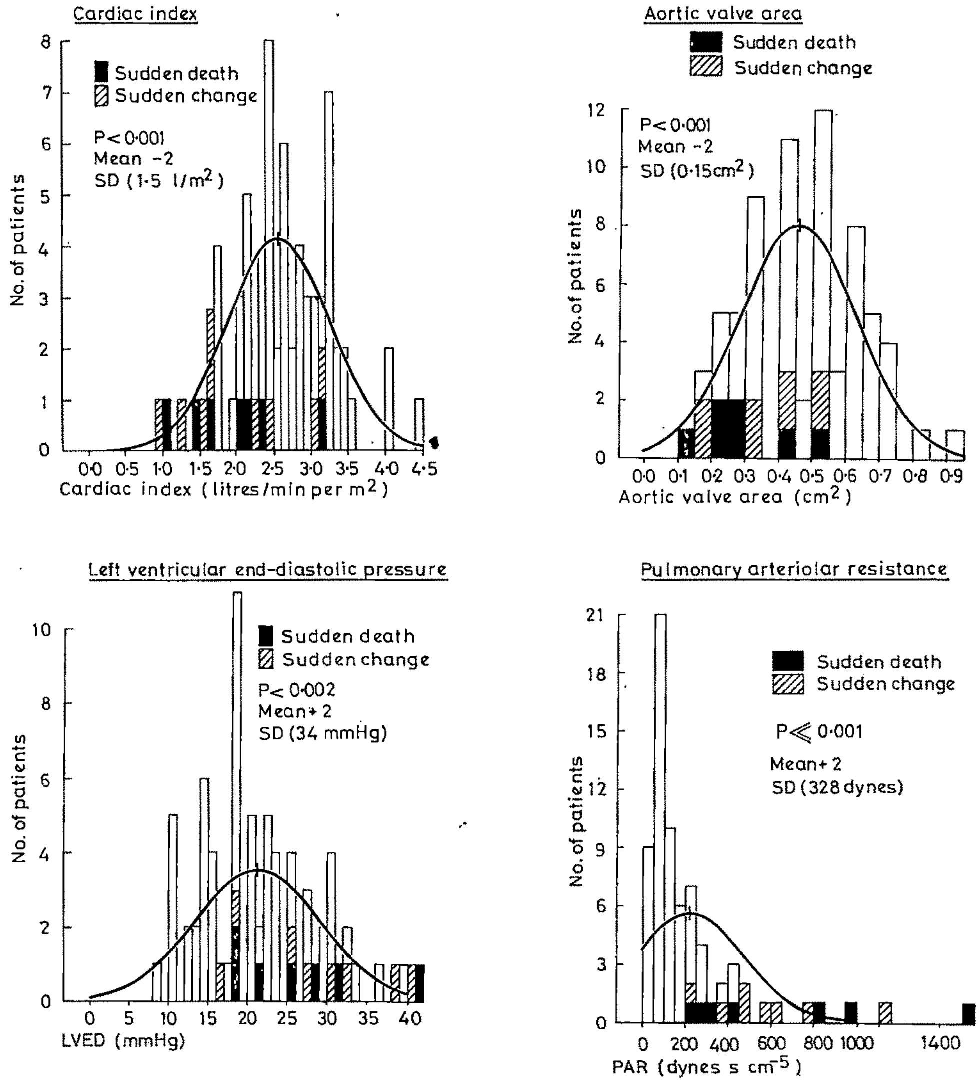

Fig. *Statistical analysis of haemodynamic indices in patients with aortic stenosis. Patients dying suddenly or deteriorating suddenly are compared with those who were clinically stable.*

emergency surgery because of a deterioration in their clinical state the mean value was raised to 47 mmHg.

Statistical analysis indicated that with sudden death or deterioration there was a significant relation to lowered cardiac index and valve area and to increased left heart filling pressures (Table 4). However, when pulmonary arteriolar resistance was analysed, statistical correlation with death or deterioration increased by one order of magnitude. Patients dying suddenly or deteriorating suddenly had a higher pulmonary arteriolar resistance than the remaining population, averaging 591 dynes as compared with 130 dynes in the stable population (Fig.). Pronounced reduction in pulmonary arteriolar resistance occurred in 3 patients restudied soon after operation (Table 5). Additionally, the cardiac index rose and left ventricular filling pressure dropped, as did left atrial mean pressure and pulmonary artery pressure.

Reversal of the ventriculoatrial gradient was found in 13 of the 15 patients in the subject group (Tables 1 and 2). However, premature closure of the mitral valve was not felt to be the cause (Basu

Table 3 *Aortic stenosis: haemodynamic values* in 72 patients*

CI	0·98	2·6	4·0	l/min
AVA	0·15	0·46	0·9	cm^2
LVEDP	8	21·2	47	mmHg
PAP	11	27	72	mmHg
PAR	13	218·9	1528	dynes cm s^{-5}

*Range and mean values.

Table 4 *Population identity: P values relating to sudden death or deterioration; statistical relation between haemodynamic events*

AVA = 0·001
CI = 0·001
LVED = 0·002
PAR $\leqslant$ 0·001

et al., 1978) since all subjects were in sinus rhythm and echocardiographic study of the mitral valve in 8 showed normal closing times. The 'reversed gradient' was felt to be the result primarily of the forceful increase in atrial contraction in end-diastole.

Discussion

Patients with aortic stenosis and congestive heart failure admittedly have a poor prognosis. In the subject group, 7 of 15 patients had severe heart failure and 5 had cardiogenic shock, occurring after catheterisation in 4 and before study in 1 patient who survived operation. In the clinically stable group, over 50 per cent had congestive failure but were well controlled medically.

Sudden death from aortic stenosis has been well correlated with left ventricular failure, and with the duration of delay between catheterisation and the time of operation (Matthews *et al.*, 1974), but neither the pathophysiological mechanisms responsible for sudden death in aortic stenosis nor the pre-mortem haemodynamics are known. Data from this study suggest that resting pulmonary hypertension caused by increased precapillary resistance may occur as a late and near-terminal manifestation of aortic stenosis and, in combination with left ventricular failure, may formidably influence prognosis. The effect of this added resistance is to increase right ventricular overload, compromising the cardiac output of an already afterloaded left ventricle. Such afterloads in series may identify a population at greater risk for sudden death. The data do not, however, prove that abnormal pulmonary vascular resistance causes death, but suggest that, together with left ventricular failure, it may be a marker for sudden death or deterioration in marginally compensated patients.

Pulmonary hypertension in disease of the left ventricle is not uncommon at rest and with exercise, and mortality, as reported by Trell (1973), increases significantly with increasing levels of pulmonary artery pressure. In prior haemodynamic studies, pulmonary hypertension in aortic stenosis has been attributed to left ventricular failure alone without precapillary vascular obstruction (Kirsch *et al.*, 1970; Trell, 1973; Matthews *et al.*, 1974). In contrast, we find that there may be pronounced pulmonary vasoconstriction in severe aortic stenosis, not unlike that seen in long-standing mitral stenosis (Gorlin *et al.*, 1951) and perhaps serving the same physiological purpose of averting pulmonary oedema at the expense of right ventricular function (Wood, 1954). Additional causes of pulmonary hypertension (Walston *et al.*, 1973) were not apparent clinically but cannot be excluded since pulmonary function studies and arterial blood gases were not uniformly performed. However, there was no history of pulmonary disease in the subject population. Arterial oxygen tensions at the time of cardiac catheterisation were mildly reduced in 3 of the subject population. Mitral stenosis was excluded by left heart catheterisation, though mitral regurgitation

Table 5 *Pre- and postoperative haemodynamics after emergency aortic valve replacement*

Case no.	*LA*	*PA*	*Ao*	*LV*	*CI*	*AVA*	*PAR*
13							
Preop.	35	112/57 ($\overline{68}$)	87/61	190/32	2·3	0·33	587
Postop. 1 mth	8	40/19 ($\overline{23}$)	148/84	172/10	3·3	1·4	184
14							
Preop.	31	72/32 ($\overline{46}$)	86/68	145/25	0·98	0·15	769
Postop. 1 wk	8	42/18 ($\overline{25}$)	83/58	103/10	2·6	1·4	309
15							
Preop.	23	97/47 ($\overline{65}$)	92/64	141/27	1·6	0·44	1159
Postop. 10 dy	12	58/29 ($\overline{36}$)	103/56	110/17	2·3	1·56	492

was not assessed angiographically.

One might properly ask why severe pulmonary hypertension and increased precapillary vascular obstruction have not previously been recognised in aortic stenosis. First, since the development of mathematical criteria for orifice area (Gorlin *et al.*, 1955), critical reduction in this index has been the primary indication for surgery in symptomatic patients. Secondly, abnormal pulmonary vascular resistance and pulmonary hypertension have seldom been reported or sought (Smith *et al.*, 1954; Pirincci *et al.*, 1961; Kirsch *et al.*, 1970; Lee *et al.*, 1970; Trell, 1973; Matthews *et al.*, 1974), and analysis of the dynamics of the pulmonary circulation has not been considered a useful criterion for assessing diseases of left ventricular outflow.

All patients clearly showed haemodynamic findings of severe aortic valvular stenosis, and operation was warranted by these criteria alone. Only the timing of the operation was in question. Fifty-seven stable patients underwent elective replacement of the aortic valve. Of these, 7 had pulmonary hypertension (mean pulmonary artery pressure 39 mmHg; mean pulmonary arteriolar resistance 222 dynes). Their pressures and resistances, though increased, were significantly lower than in the unstable group. Therefore, not all patients with pulmonary hypertension may need emergency surgery. However, the magnitude of pulmonary resistance changes may be useful in choosing candidates for urgent operation.

Our experience suggests an arbitrary cutoff point where a critical rise in pulmonary arteriolar resistance exists and where urgent surgery should be considered. Ten patients with pulmonary arteriolar resistances over 350 dynes suddenly died or became seriously ill. Using this arbitrary cutoff value, 4 subjects died but 6 survived emergency operation.

Clinically terminal patients with aortic stenosis need no haemodynamic studies to confirm the severity of their disease. However, we emphasise that of the 7 patients who died (Table 1), 3 were stable enough to be discharged for elective surgery and 1 died suddenly and unexpectedly while awaiting hospital discharge. Of the 8 patients who underwent emergency valve replacement (Table 2), 4 were in congestive failure and 2 were in cardiogenic shock. Of these patients, 5 would not have been selected for urgent surgery had not the relation of abnormal pulmonary vascular resistance to sudden death been known.

We, therefore, believe that severe pulmonary hypertension caused by increased precapillary resistance may exist as a late physiological manifestation of severe aortic stenosis either in patients who appear stable or who are critically ill. In conjunction with severe left ventricular failure, this finding relates to sudden death or sudden clinical deterioration. Rapid and successful surgical intervention may prevent death in these patients. The data suggest that patients with assumed end-stage disease can survive operation and improve haemodynamically.

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Comparison of cathodal, anodal, and bipolar strength-interval curves with temporary and permanent pacing electrodes[1]

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SUMMARY Acute animal experiments indicate that ventricular vulnerability to fibrillation or multiple premature contractions is greater during bipolar or anodal stimulation than with unipolar cathodal (with electrodes of equal cathodal and anodal surface area) because the anodal and bipolar absolute refractory periods are shorter, enabling easier excitation in the vulnerable period. To compare the relative safety of stimulation with various commercial electrodes, strength-interval curves were determined in patients during the initial period after electrode implantation (acute studies) and after a few years of pacing (chronic studies). In 9 of 10 acute studies in patients with permanent bipolar electrodes (anode surface area 4·4 times cathode) and in 9 of 10 chronic studies in patients with bipolar electrodes, the unipolar cathodal and bipolar refractory periods were equal. However, in 7 of 12 patients with temporary bipolar electrodes (equal anodal and cathodal surface areas) and in 2 out of 20 acute and chronic studies in patients with permanent bipolar electrodes, the bipolar refractory periods were significantly shorter than cathodal because of anodal stimulation at the proximal electrode. Under appropriate physiological conditions and competitive pacing, these patients would be more vulnerable to arrhythmias with bipolar stimulation than with unipolar cathodal. To decrease that risk, the anodal surface area should be 5 to 7 times the cathodal, or the anode should be removed from the ventricle, especially for temporary pacing in circumstances of high vulnerability to arrhythmias.

Arrhythmias initiated by electrical stimulation of the heart have been well documented in animals and in man (Wiggers and Wegria, 1940; Brooks *et al.*, 1955; Bilitch *et al.*, 1967). The probability of occurrence of pacemaker induced ventricular fibrillation or tachycardia is small but increases in the presence of specific physiological and pharmacological factors and during stimulation about the T wave and in patients with bipolar as compared with unipolar electrodes (Preston, 1973). The electrophysiological basis for the differences in arrhythmia susceptibility with unipolar cathodal, unipolar anodal, and bipolar stimulation has been shown in animals to result from the dissimilarities in the maximum prematurity of stimulation that can occur (Mehra *et al.*, 1977). In an acutely ischaemic ventricle, the vulnerable period for fibrillation or multiple premature contractions starts at the end of the absolute refractory period and ends at a certain time thereafter. As the refractory periods with anodal and bipolar stimulation are shorter than with cathodal (when equal surface area cathode and anode are used), a response is possible earlier in the cardiac cycle with anodal or bipolar stimuli and their vulnerable periods are, therefore, longer.

In the present study, we evaluate the possible clinical differences between cathodal and bipolar stimulation in relation to ventricular vulnerability. Despite the prevalence of non-competitive pacing, circumstances arise because of pacemaker malfunction or during acute myocardial infarction (Chatterjee *et al.*, 1970) when competition between pacemaker stimuli and spontaneous cardiac rhythm occurs.

To compare the maximum prematurity of stimulation possible with unipolar cathodal, unipolar anodal and bipolar stimuli, the cardiac excitation threshold was measured during the cardiac cycle,

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and strength-interval curves were plotted, in patients with intracardiac electrodes. Two studies were undertaken. In the first, unipolar cathodal and anodal strength-interval curves were compared. Though unipolar anodal stimulation is not used clinically, these data helped to explain the effect of the inadvertent unipolar anodal stimulation that can occur during temporary pacing. In the second study, bipolar and unipolar strength-interval curves were compared.

Patients and methods

Strength-interval curves were derived for different modes of stimulation (Fig. 1) in 43 paced patients. Informed consent was obtained from all patients. Extremely sick patients and those suffering from acute myocardial infarction were excluded from the study. The 'acute studies' were performed with implantable (permanent) electrodes at the time of insertion and with 'temporary' electrodes at insertion or within a few days thereafter. The 'chronic studies' were made on patients with electrodes in use for between 1 and 5 years, during pulse-generator replacement. The electrodes were either unipolar or bipolar and differed in the stimulating surface areas (Table 1). During unipolar stimulation with an implantable electrode, the subcutaneous pulse generator site was used for the indifferent electrode while for the temporary electrodes, a surgical steel wire inserted in the skin of the right pectoral region acted as the indifferent electrode.

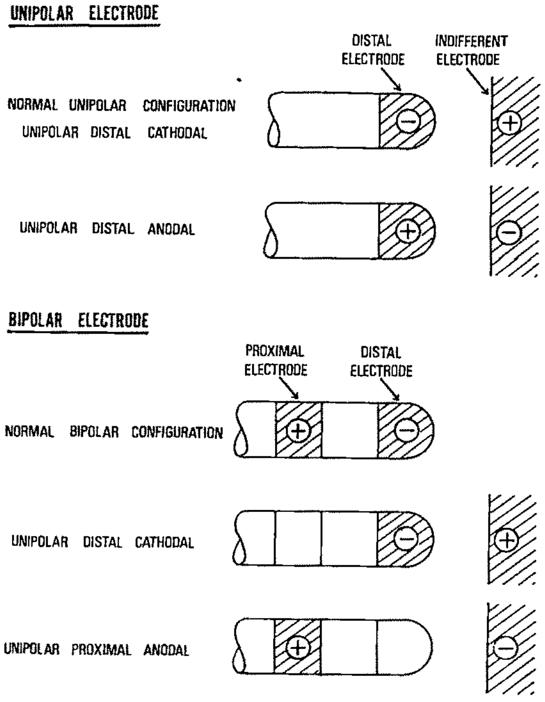

Fig. 1 *Different modes of stimulation for which the strength-interval curves were determined with unipolar and bipolar electrodes.*

Most patients were paced at 80 beats/minute via their right ventricular electrodes. In some the pacing rate was 90 to 100 beats per minute to eliminate competition. Cathodal pacing at twice the current excitation threshold was used for all studies with the test pulse occurring every seventh beat. From the normally excitable period, the test pulse delay was progressively shortened in 20 ms steps and at each stimulus interval the cathodal, anodal, or bipolar threshold of excitation was measured to an accuracy of 0·1 mA. As the stimulation threshold rose during the relative refractory period, steps of 10 ms duration or less were used. To measure threshold, the test pulse was progressively decreased in amplitude with two applications of the test pulse at each current. Threshold was the minimum test current which, during each of its two applications, resulted in a captured beat. The stimulator[1] delivered constant current pulses of 1·0 ms duration with a maximum output of 9 mA. Resuscitation equipment was always kept available in case of any serious arrhythmias.

Results

(a) UNIPOLAR CATHODAL AND ANODAL STRENGTH-INTERVAL CURVES

Unipolar cathodal and anodal strength-interval curves were plotted in 8 acute and 9 chronic cases (Fig. 2 and 3). In the acute studies, the refractory periods for anodal stimulation were usually shorter than for cathodal at most stimulus currents, while in the chronic studies the anodal refractory periods were usually longer. However, in one acute study, the cathodal refractory period was shorter than anodal at lower stimulus currents (Fig. 2b), and in 2 chronic studies, the anodal refractory periods became shorter at higher stimulus currents (Fig. 3b). In both acute and chronic studies, the mean difference in refractory periods was expressed as a function of current density rather than stimulus current so that it was possible to compare electrodes of different surface area (Table 2). In the acute studies the difference in refractory periods averaged 7 to 9 milliseconds at most current densities. In the chronic studies the anodal refrac-

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[1] Devices Sales Ltd, Hertfordshire, England

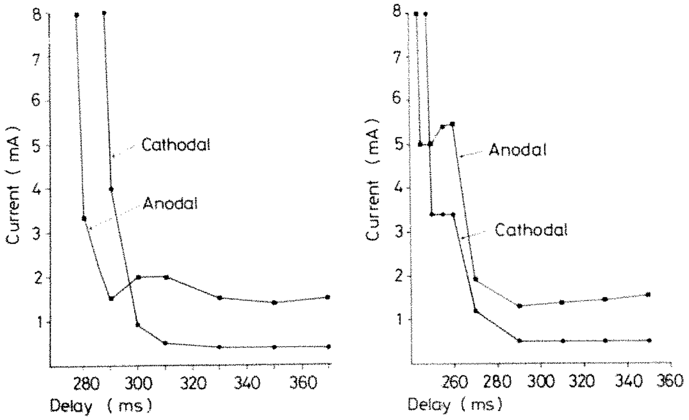
Table 1a *Electrodes used for determining unipolar distal cathodal and anodal strength-interval curves*

	Manufacturer	*Electrode type*	*Distal area (mm²)*	*No. of cases*
(1) Acute	Medtronic*	6907	11	5
	Medtronic	6901	11	3
				8
(2) Chronic	Cordis†	2mm	12	5
	Medtronic	6901	11	1
	Medtronic	5819	11	1
	Cordis	4mm	28	1
	Medtronic	5816	85	1
				9

Table 1b *Electrodes used for determining bipolar, unipolar distal cathodal, and unipolar proximal anodal strength-interval curves*

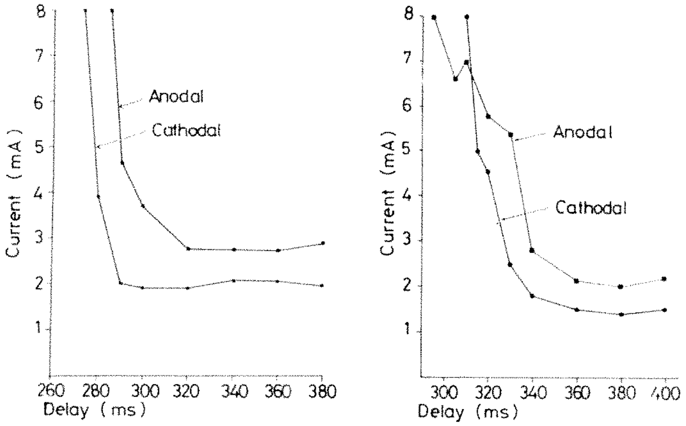
	Manufacturer	*Electrode type*	*Distal area (mm²)*	*Proximal area (mm²)*	*No. of cases*
(1) Acute	Medtronic	6901	11	48	10
	Cordis	Temp.	12·5	12·5	12
					22
(2) Chronic	Medtronic	6901	11	48	5
	Medtronic	5819	11	48	1
	GE‡	A2070	11	43	2
	Medtronic	5816	85	80	2
					10

* Medtronic Inc., Minneapolis, Minn.
† Cordis Corp., Miami, Florida
‡ General Electric Co., Milwaukee, Wisconsin



(a) (b)

Fig. 2 *(a) Typical unipolar cathodal and anodal strength-interval curves obtained during an acute study in a patient with a unipolar electrode (Medtronic 6907; surface area 11 mm²). The ordinate represents the excitation current threshold in milliamperes and the abscissa the delay of the test stimulus as measured from the heart rate determining stimulus. Note that the anodal refractory periods are shorter than cathodal for most stimulus currents. (b) Atypical unipolar cathodal and anodal strength-interval curves obtained during an acute study on a patient with a 6097 electrode.*



(a) (b)

Fig. 3 *(a) Typical unipolar cathodal and anodal strength-interval curves obtained during a chronic study in a patient with a 33-month-old unipolar electrode (2 mm electrode; surface area = 12 mm²). Note the longer anodal refractory periods. (b) Atypical unipolar cathodal and anodal strength-interval curves obtained during a chronic study with a 2 mm electrode.*

Table 2 *Difference between unipolar cathodal and anodal refractory periods (△RP) determined in acute and chronic studies*

No. of cases	*Area (mm²)*		*Current density (mA/cm²)* 20	30	40	50	60	70
(A) *Acute*		ΔRP (ms)						
8	11	Mean	4	7	7	9	9	9
		SEM*	2·8	3·5	2·8	1·1	1·1	1·1
(B) *Chronic*		ΔRP (ms)						
8	11, 12	Mean	−8	−8	−8	−8	−4	−3
		SEM	2·6	2·6	1·9	1·5	3·0	3·8

* SEM = Standard error of the mean.

tory periods were of greater duration than cathodal by an average of 8 to 9 milliseconds. The characteristic 'dip', which represents a narrow region early in the cardiac cycle during which the anodal current threshold is significantly less than in the subsequent interval (Van Dam *et al.*, 1956; Cranefield *et al.*, 1957), was observed in all acute (Fig. 2) and in only 1 of the 9 chronic studies (Fig. 3b).

(b) BIPOLAR AND UNIPOLAR STRENGTH-INTERVAL CURVES

Bipolar, unipolar distal cathodal, and unipolar proximal anodal strength-interval curves were plotted in 22 acute studies. Ten were obtained using the Medtronic model 6901 electrode (tip surface area 11 mm² and proximal 48 mm²) and 12 with the temporary 4F Cordis electrode (proximal and the distal areas equal, each 12·5 mm²). The results from the 2 studies were very different. With 9 of 10 model 6901 electrodes (90%) the bipolar and unipolar cathodal refractory periods were equal, as the bipolar strength-interval curve was unaffected by proximal anodal stimulation because of its high excitation threshold and therefore followed the lower of the unipolar distal cathodal and proximal anodal strength-interval curves (Fig. 4). In 7 of the 12 cases (58%) with temporary electrodes, the bipolar refractory periods were significantly shorter than unipolar cathodal because of low anodal excitation thresholds at the proximal electrode. Thus, in the case shown in Fig. 5a, at a delay shorter than 285 ms the anodal threshold was lower than the cathodal so that bipolar excitation occurred from the proximal anode to yield equal anodal and bipolar refractory periods. In all 7 cases the 'dip' in the anodal strength-interval curve caused the earlier bipolar excitation, with a 9 ms mean difference between cathodal and bipolar refractory periods at various current densities

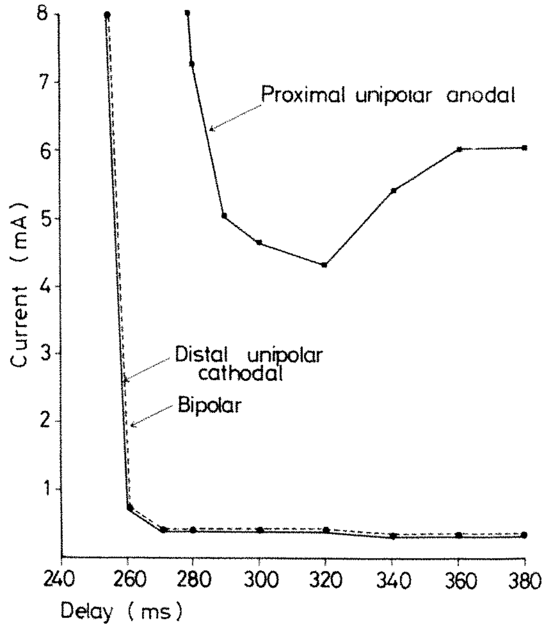


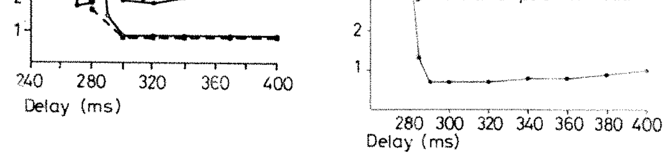
Fig. 4 *Unipolar distal cathodal, unipolar proximal anodal, and bipolar strength-interval curves obtained during an acute study in a patient with a 6901 bipolar electrode (case 29). Note that the bipolar and unipolar cathodal curves coincide.*

(Table 3). With the remaining 5 temporary electrodes (42%), equal duration cathodal and bipolar refractory periods existed up to 9 mA as anodal excitation could not be elicited early in the cardiac cycle (Fig. 5b). The only arrhythmia produced by premature stimulation close to the refractory period was a single unstimulated premature contraction in 2 cases.

In chronic studies with bipolar electrodes, cathodal and bipolar strength-interval curves obtained were similar to those obtained in the acute studies with permanent electrodes. Cathodal and bipolar refractory periods were equal in 9 of the 10 cases (90%) (Fig. 6a). In 7 of the 10 cases, anodal stimulation up to 8 mA did not initiate excitation at the proximal electrode. With only one model 6901 electrode was the bipolar refractory period shorter than the cathodal (Fig. 6b).

Discussion

Animal experiments and clinical experience indicate that the probability of inducing an arrhythmia in a vulnerable myocardium is increased by increasing prematurity of a suprathreshold stimulus (Bilitch *et al.*, 1967; Mehra *et al.*, 1977). The present 'acute' study shows that greater prematurity of stimulation occurs with a bipolar stimulus than with a unipolar cathodal stimulus with temporary



(a) (b)

Fig. 5 *(a) Unipolar distal cathodal, unipolar proximal anodal, and bipolar strength-interval curves obtained during an acute study in a patient with a temporary bipolar electrode (case 39). The bipolar and unipolar anodal refractory periods are equal and shorter than unipolar cathodal. (b) Strength-interval curves determined with the same electrode in another patient (case 35). In this case stimulation at the proximal anode does not shorten the bipolar refractory period.*

Table 3 *Difference between cathodal and bipolar refractory periods ($\triangle RP$) determined in patients with temporary electrodes*

No. of cases	*Distal and proximal area (mm²)*		*Current density (mA/cm²)* 20	30	40	50	60	70
		ΔRP (ms)						
7	12·5	Mean	9	9	9	9	9	9
		SD	10	7	5	5	6	6
		SEM	3·8	2·6	1·9	1·8	2·1	2·4

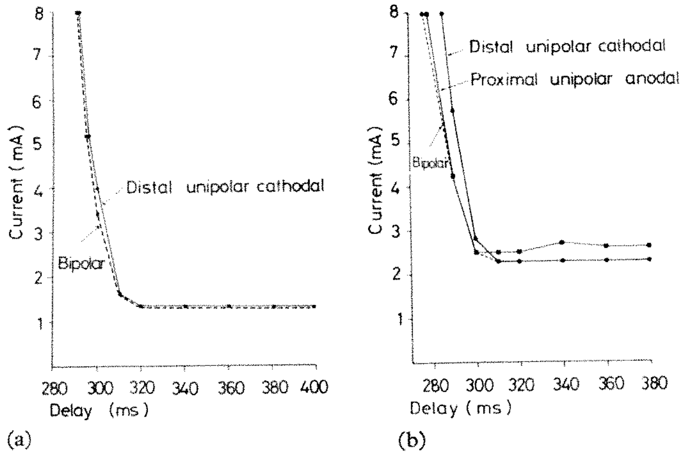


Fig. 6 (*a*) *Typical strength-interval curves obtained during a chronic study in a patient with a 6901 bipolar electrode. Excitation could not be elicited with anodal stimulation from the proximal electrode site.* (*b*) *An atypical case with a 6901 electrode (case 11). Note that the bipolar and anodal refractory periods are shorter than cathodal.*

electrodes which have equal surface area cathode and anode (each 12·5 mm² in this instance). With such electrodes, shorter bipolar refractory periods were obtained in 7 of 12 cases, as a result of earlier anodal stimulation. In 10 acute and 8 chronic studies with permanent electrodes, in which the anodal surface area was 4 to 4·5 times the cathodal, shorter bipolar refractory periods were observed in only one patient in each group. The difference between temporary and permanent electrodes is statistically significant ($P < 0.05$).

The differences between strength-interval curves of the various bipolar electrodes can be explained on the basis of the strength-interval curves determined with unipolar electrodes. In 7 of 12 cases with temporary bipolar electrodes, anodal and cathodal curves were similar to those obtained with unipolar electrodes. In both, shorter anodal refractory periods and the 'anodal dip' were present. In the others (5 of 12) the anodal refractory periods were longer. This may be the result of a large tissue-electrode separation which can increase the stimulus current required for threshold, resulting in a shift of the anodal strength-interval curve upward and making the anodal refractory periods longer than cathodal. The longer anodal refractory period found in most acute and chronic studies with permanent electrodes was probably caused by the 4·4 times larger anodal than cathodal surface area. Even when the 2 surface areas were equal in some permanent bipolar electrodes, unipolar chronic strength-interval curves show that the anodal refractory period would still be expected to be longer than the cathodal.

DESIGN OF SAFER PACEMAKER SYSTEMS

The 7 temporary electrodes in which greater prematurity of stimulation occurred with bipolar rather than with cathodal stimulation could be made safer by increasing the duration of the bipolar refractory period so that it is equal to the cathodal. As current density determines excitation threshold (Furman *et al.*, 1975), this can be accomplished by an increase of the anodal surface area. To make bipolar and cathodal refractory periods equal up to 8 mA of stimulus current the minimum desirable ratio of anodal to cathodal surface area was calculated to be between 1·6 and 4·2. Another way of avoiding the problem of shorter bipolar refractory periods is to move the anode away from the ventricle (Preston, 1974), but this solution may cause problems related to the position of the indifferent terminal.

In only 2 out of 20 acute and chronic studies with permanent electrodes were the bipolar refractory periods shorter than cathodal. In order to make the refractory periods equal with stimulus currents up to 8 mA in these cases, the anodal surface area would have to be at least 7·0 times the cathodal in an acute study and 6·6 in a chronic study. All these results indicate that an anodal to cathodal surface area ratio of 5 to 7 is desirable for the design of safe temporary and permanent bipolar electrodes.

Other factors also affect the duration of the absolute refractory period and hence the maximum prematurity of a suprathreshold stimulus. Strength-interval curves indicate that lower current densities and short pulse duration stimuli would decrease the probability of precipitating arrhythmias by increasing the shortest stimulus coupling interval (Brooks *et al.*, 1955). The maximum stimulus prematurity with suprathreshold stimuli is also significantly influenced by the time elapsed since electrode insertion, probably as a result of the development of inexcitable tissue around the electrode, which increases the effective surface area and reduces the current density in the excitable tissue (Roy *et al.*, 1968; Tarjan, 1973; Furman *et al.*, 1975). In our chronic studies, the cathodal refractory periods at 70 mA/cm^2 and 80 beats/minute were 296 ± 19 ms as opposed to 268 ± 27 ms in acute studies with permanent electrodes ($P < 0{\cdot}05$).

DOCUMENTED CASES OF VENTRICULAR FIBRILLATION AND TACHYCARDIA

The data presented help to explain the 30 documented (with the onset illustrated) cases of pace-

Table 4 *Documented cases of arrhythmias induced by pacemaker stimuli*

Case no.	*Investigators*	*Arrhythmia**	*Mode†*	*Electrode data*		
				Position‡	*Type§*	*Age¶*
1	Bertrand *et al.* (1967)	VF	B	Epi.	P	1 d††
2	Bilitch *et al.* (1967)	VF	B	Endo.	T	1 d
3	Burgess *et al.* (1970)	VF	B**	Endo.	T	4 d
4	Castellanos *et al.* (1970)	VT	B	Endo.	T	1 d
5	Castellanos *et al.* (1970)	VT	B	Epi.	P	18 m
6	Castellanos *et al.* (1970)	VT	B	Endo.	T	1 d
7	Castellanos *et al.* (1970)	VF	B	Endo.	T	1 d
8	Elmquist *et al.* (1963)	VT	B	Epi.	P	1 d
9	Forfang and Lippestad (1971)	VT	B	Endo.	T	1 d
10	Grondin *et al.* (1967)	VT	B	Epi.	P	11 d
11	Jensen *et al.* (1966)	VT	B	Endo.	P	1½ m
12	Koch and Wiessmann (1971)	VF	B	Epi.	P	54 m
13	Lanoy and Picart (1973)	VF	B	—	P	20 m
14	Lemberg *et al.* (1969)	VT	B	Endo.	T	1 d
15	Lemberg *et al.* (1969)	VT	B	Endo.	—	1 d
16	Lemberg *et al.* (1969)	VF	—	Endo.	T	1 d
17	Lemberg *et al.* (1969)	VF	—	Endo.	—	1 d
18	Lemberg *et al.* (1969)	VT	—	Endo.	—	1 d
19	Lumia and Rios (1973)	VT	B	Endo.	T	1 d
20	Martinoli (1970)	VT	B	Endo.	T	1 d
21	Martinoli (1970)	VT	B	Endo.	T	—
22	Overbeck and Buchner (1965)	VT	B	—	—	—
23	Robinson *et al.* (1965)	VF	B	Epi.	P	16 m
24	Roth *et al.* (1971)	VF	B	Endo.	T	1 d
25	Roth *et al.* (1971)	VT	B	Endo.	T	1 d
26	Tavel and Fisch (1964)	VT	B	Epi.	P	1 d
27	Zipes (1975)	VF	U	—	P	22 m
28	Burchell and Meredith (1969)	VT	—	—	T	1 d
29	Schatz *et al.* (1975)	VF	B	Endo.	T	1 d
30	Batchelder and Zipes (1975)	VF	—	—	T	—

Key:
* VF, ventricular fibrillation; VT, ventricular tachycardia.
† B, bipolar; U, unipolar cathodal.
‡ Endo., endocardial electrode; Epi., epicardial electrode.
§ P, permanent electrode; T, temporary electrode.
¶ Time since electrode implantation, d: days; m: months
** Personal communication.
†† 1 d indicates less than or equal to 1 day.

maker induced ventricular tachycardia or fibrillation. The electrode type was mentioned in 25 of these 30 cases, and was bipolar in all except one (Table 4). It is quite likely that these are only a small portion of the total number of such occurrences. Of the 25 episodes, 13 occurred with temporary endocardial electrodes, almost all of which have equal area cathode and anode. Temporary electrodes are commonly used during acute myocardial infarction, but even in these patients use of the bipolar rather than the unipolar mode of stimulation may have been the important factor in inducing arrhythmias. The possible role of bipolar pacing is further emphasised as 8 of 10 cases of ventricular fibrillation/tachycardia with permanent pacemakers occurred with epicardial electrodes with equal area cathode and anode. Of the remaining 2, 1 occurred with a unipolar cathodal and the other with a bipolar endocardial electrode. In all the documented cases, a pacemaker stimulus from an asynchronous or a malfunctioning demand pacemaker initiated the arrhythmia when it fell on the T wave of an intrinsic beat. Another potentially dangerous situation can arise when a demand pacemaker is switched on. The first stimulus (which in many models does not follow a sensed cardiac cycle) may inadvertently fall within the vulnerable period and precipitate arrhythmias as in cases 19, 28, and 29 (Table 4).

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Blood volume in angina pectoris

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SUMMARY Blood volume was measured in 60 consecutive male patients with disabling angina pectoris undergoing preoperative investigation for coronary bypass surgery. Of these patients, 58 had a lower blood volume than predicted. There was a decrease in blood volume of 21 per cent (1·3 litres) from the predicted normal value ($P < 0·001$). Seventeen per cent of the patients were on diuretics, 30 per cent were on digitalis, and 48 per cent were on beta-blocking drugs at the time of the study. There was no correlation between this medical treatment and the deviation in blood volume. In patients without signs of myocardial insufficiency the decrease in blood volume was most prominent, while in those with an enlarged heart and a raised left ventricular preload (at rest) the deviation was less.

Total blood volume is an important determinant of optimal cardiac function. Thus, increase in blood volume along with physical training is an adaptation and prerequisite for the increase in cardiac performance (Holmgren *et al.*, 1960). Several pathological conditions also influence the blood volume. Congestive heart failure is accompanied by an increase in total blood volume (Hedlund, 1953). Physical deconditioning resulting from long bed rest causes a decrease in the blood volume (Saltin *et al.*, 1968). Patients with valvular heart disease with no signs of heart failure, however, have a normal blood volume (Holmgren *et al.*, 1957). Patients with ischaemic heart disease are very sensitive to changes in magnitude and distribution of blood volume and particularly pulmonary blood volume. Shifting blood from the peripheral vascular bed to the lungs by changing from a sitting to a supine position will aggravate the symptoms of angina pectoris (Lecerof, 1971).

It is generally believed that the relief of angina by nitrates is caused by peripheral pooling accompanied by a decrease in ventricular volume (Mason and Braunwald, 1965; Williams *et al.*, 1965). In a study from this laboratory on the haemodynamic effects of beta-blockers in patients with angina pectoris it was found that total blood volume was low (Jonsson *et al.*, 1973; Åström *et al.*, 1976). The present investigation deals with a more elaborate study of blood volume in patients with angina pectoris accepted for preoperative investigation for bypass surgery.

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Subjects and methods

Studies were made on 60 male patients with disabling angina pectoris. They were all assessed before operation for coronary bypass. Significant coronary artery disease was verified with selective angiography. The criteria for angina pectoris were typical chest pain elicited by effort and verified during an exercise test with a 6-lead chest electrocardiogram. Cardiac catheterisation was also performed in the majority of patients both at rest and during exercise.

Blood volume was calculated from the total amount of haemoglobin (THb), determined with the alveolar CO method of Sjöstrand (Sjöstrand, 1948; Holmgren, 1969) and haemoglobin concentration with correction to body haematocrit by a factor of 0·91. This method was used in 53 patients; in 7 patients the dilution method with radio-iodinated serum albumin (131 RIHSA) and a Volumetron was used (Williams and Fine, 1961). No significant difference was found between these two methods (A. Holmgren, 1976, unpublished observations). The age of the patients ranged between 34 and 64 years. Fifty per cent of the patients had had a previous myocardial infarction either from history or from the electrocardiogram. Fourteen patients (23%) had a normal resting electrocardiogram but all showed ST depression on exercise.

Thirty per cent of the patients were being treated with digitalis, 17 per cent with diuretics, and 48 per cent with beta-adrenergic blocking agents when referred to the clinic. In all patients the beta-blockade was stopped during the hospital stay and in most of them also the other drugs. Forty-nine (82%) patients later went to bypass surgery.

Results

The normal value for THb in men in our laboratory is 10·46 ± 1·16 g/kg body weight and for blood volume 78·7 ± 5·9 ml/kg body weight (Holmgren, 1969). The blood volume in the patients with ischaemic heart disease averaged 4·74 ± 0·73 litres or 62·1 ± 7·8 ml/kg body weight. This is 1·3 litres less than predicted from the body weight. This difference of −21·1 per cent was highly significant ($P < 0·001$). In all patients except 2 the blood volume was lower than predicted (Fig. 1). The THb averaged 8·17 ± 1·17 g/kg body weight which is 21·9 per cent less than predicted ($P < 0·001$).

The patients with increased heart volumes tended to show smaller deviations from predicted blood volume (Fig. 2). All those with blood volumes below 25 per cent of predicted had normal heart volumes (<500 ml/m^2 body surface area). Left ventricular filling pressure, measured as mean wedge pressure, was normal in most patients with angina pectoris at rest. However, those with wedge pressures above 15 mmHg had a smaller decrease in blood volume than the others (Fig. 3) and were within the normal range though still on the negative side. Of 60 patients, 46 were studied during heart catheterisation both at rest and exercise, and 41 (89%) of these had an abnormal increase in wedge pressure during exercise (Fig. 4).

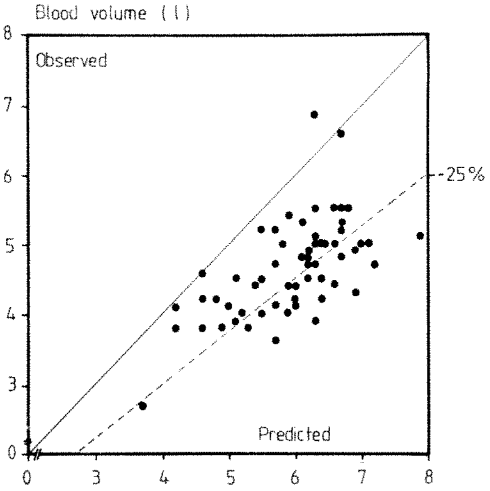

Fig. 1 *Blood volume in litres in patients with angina pectoris. Observed values (y axis) are given in relation to predicted (x axis) values. The 25 per cent reference line is shown.*

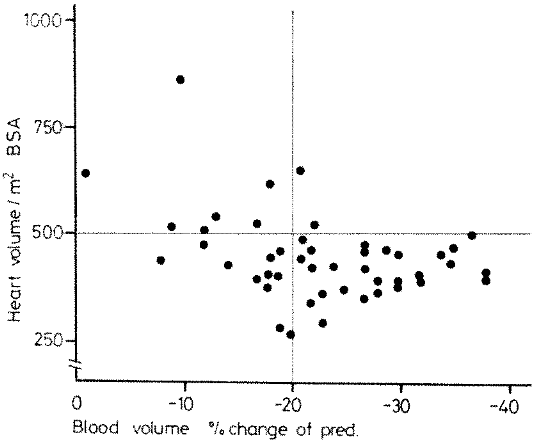

Fig. 2 *Heart volume (ml/m^2 body surface area) in relation to the relative decrease in blood volume from the predicted value (47/60 patients). Upper heart volume and lower blood volume normal limits are shown in straight lines.*

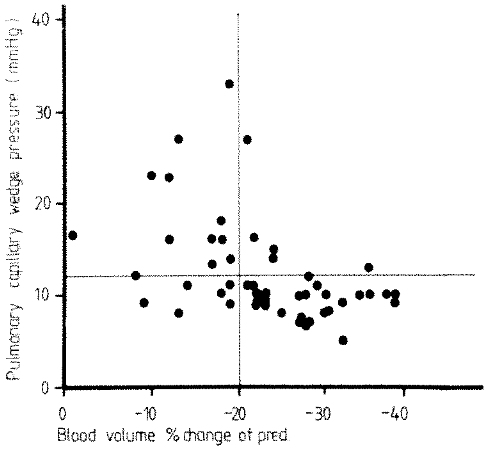

Fig. 3 *Pulmonary capillary wedge pressure in relation to the relative decrease in blood volume from the predicted value. Upper pulmonary capillary wedge pressure and lower blood volume normal limits are shown in straight lines.*

Discussion

Blood volume in patients with disabling angina pectoris was found to average 79 per cent of that predicted. To our knowledge this has not been reported earlier. Gábor *et al.* (1976) have described a slight increase in blood volume in patients with ischaemic heart disease uncorrelated to angina pectoris.

The effect of medical treatment might have influenced our results. After long-term treatment

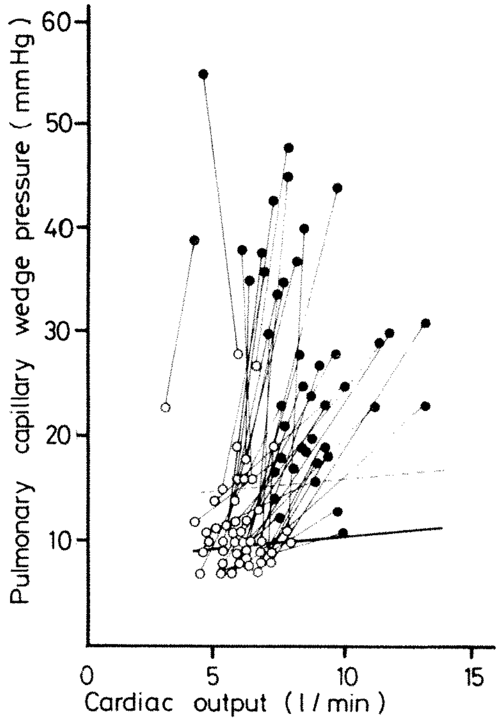

Fig. 4 *Pulmonary capillary wedge pressure at rest* (○) *and during work* (●) *in relation to the cardiac output. Normal regression line is drawn.*

with beta-blockade both a decrease in plasma volume (Tarazi *et al.*, 1971) and no change in plasma volume (Sederberg-Olsen and Ibsen, 1972; Hesse *et al.*, 1974) have been reported. However, we found no difference in blood volume between those who had been treated with beta-blockade and those who had not. Neither were there any differences between the groups on diuretics (17%) or digitalis (30%) and those without.

The majority of patients with angina pectoris were found to have normal end-diastolic left ventricular pressure at rest if not complicated by previous large myocardial infarction. However, during exercise when chest pain was precipitated the filling pressure of the left ventricle increased conspicuously, as a sign of acute reversible myocardial insufficiency.

Atrial receptors, when stimulated acutely, are known to cause increase in water and salt diuresis (Goetz *et al.*, 1975). However, Greenberg *et al.* (1973) have shown that in the presence of heart failure these receptors are depressed in their function. One might, therefore, expect an increase in blood volume in heart failure, or raised end-diastolic volume, and this correlates with our finding that the blood volume reduction was less in the patients with heart failure.

Left ventricular receptors are stimulated by acute ventricular dilatation and such stimulation reduces renal sympathetic nervous activity and might, therefore, by renal vasodilatation lead to a diuresis (Öberg and White, 1970). In man, Bennett *et al.* (1977) have shown that there is an unexpected diuresis in the acute and early stage of left ventricular failure after myocardial infarction, but this does not persist. It might, therefore, be argued that in patients with angina who do not show a chronic rise in end-diastolic pressure or an enlarged heart, the constant short-lasting acute pressure rises associated with angina might lead to diuresis and hence to a reduction in blood volume (Sleight and Widdicombe, 1965).

Parker *et al.* (1970) have shown that acute phlebotomy relieved angina pectoris during pacing and normalised ventricular function. The homeostatic function of this reduction in blood volume would be to reduce the effect of the acute reversible myocardial insufficiency causing overdistension of the ventricle.

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Doerr's theory of morphogenesis of arterial transposition in light of recent research

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SUMMARY Doerr's theory of the morphogenesis of transposition is discussed with special reference to recent studies by Goor and co-workers and Anderson and associates. The views advanced by all these authors coincide in three points: (a) the description of the reorganisation process occurring at the arterial end of the embryonic heart (a process called by Doerr vectorial bulbus rotation); (b) the pathogenetic interpretation of transposition as the result of an arrest of vectorial bulbus rotation; (c) the recognition of a teratological series or spectrum of anomalies pathogenetically related to transposition. Vectorial bulbus rotation is explained mainly as the result of three largely simultaneous events: bulbar shift, bulbus torsion, and truncus torsion. The spectrum of anomalies related to transposition appears as a close-knit series. Bulbar retraction does not seem to be a necessary condition for the connection of the aorta to the left ventricle.

During the 1970's, Goor and associates in the United States (Goor *et al.*, 1972; Goor and Edwards, 1973; Goor and Lillehei, 1975) and Anderson *et al.* (1974a, b) in Britain have developed similar theories concerning the morphogenesis of transposition, which coincide in their main features with that formulated by Doerr 26 years ago (Doerr, 1952). This concordance of 3 independent sources is the more significant, since Doerr's contributions to the subject (Doerr, 1952, 1955a, b, 1960, 1970) seem to have been unknown to the later authors. There is also a remarkable similarity in the arguments used by Doerr (1938, 1943) and by Anderson's group (Anderson *et al.*, 1974a; Macartney *et al.*, 1976) to refute the pathogenetic concept of the straight bulbotruncal septum (Rokitansky, 1875) which in recent years has been postulated by de la Cruz and Pio da Rocha (1956) and de la Cruz *et al.* (1959, 1967, 1971).

Agreement exists on 3 essential points:
(1) The morphological features of the reorganisation occurring at the arterial end of the embryonic heart, a complex process denoted by Doerr *vectorial bulbus rotation* (see Fig.); (2) an arrest of this process as the main pathogenetic mechanism causing transposition; and (3) the existence of a teratological series, or spectrum, of anomalies pathogenetically related to transposition.

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However, Anderson and associates depart from Doerr and from Goor and co-workers in assigning a similar significance to bulbar shrinkage as bulbar atrophy has in Keith's theory (1909), to which Van Praagh's conal growth hypothesis (Van Praagh and Van Praagh, 1966, 1967; Van Praagh *et al.*, 1967, 1971) is also related (cf. Anderson *et al.*, 1974a; Chuaqui and Bersch, 1973). But Van Praagh's concept of *conal inversion* (Van Praagh and Van Praagh, 1966)—(unfortunately, Goor and associates use the same expression with a very different meaning, namely that of the normal bulbotruncal torsion)—shows some relation to Pernkopf and Wirtinger's belief in the inverse development of the septum bulbi as the cause of transposition (Pernkopf and Wirtinger, 1933, 1935; Wirtinger, 1937). In fact, according to Van Praagh's definition of the conus (Van Praagh and Van Praagh, 1966), the position of the great arteries depends also on how the bulbar septum develops. This is why the objections of Goor and Edwards (1973) to the conal growth hypothesis are also valid with respect to the concept of (using Doerr's expression) the *septatio aberrans transponans bulbi*. With almost the same words as those used by Doerr (1955a), they conclude that transposition is determined before the bulbar septum develops, and that the presence or absence of a conus is incidental rather than causal. As for the contribution of Pernkopf and Wirtinger it is especially important to distinguish between its

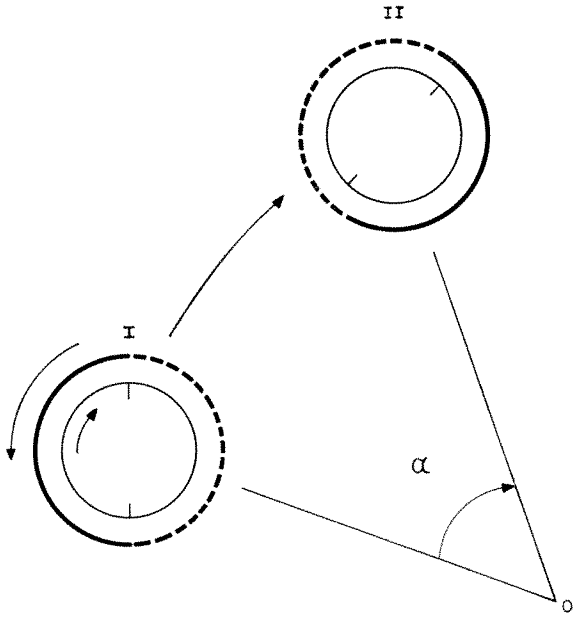

Fig. *Diagram of the vectorial bulbus rotation (caudal view; ventral: top of the figure). I: initial state, II: end state. Outer circles: bulbotruncal orifice (solid line: aortic bed; broken line: pulmonary bed); inner circles: bulbometampullar orifice. α: bulbus displacement. O: a point of reference dorsal to the bulbotruncal segment. The combination of rotation of the bulbus around its long axis and rotation around the fixed point O resembles movement of a planet round the sun; hence the term* vectorial *bulbus rotation.*

descriptive and its interpretative aspects, the former having been widely confirmed by several authors, including Doerr, but the latter representing the antithesis to Doerr's views (for a detailed discussion of this topic, see Goerttler, 1963).

Thus, viewed historically, theories on transposition have evolved in a cyclical manner, classical pathogenetic ideas re-emerging to be argued on a more secure basis, though Spitzer's phylogenetic theory (1923), reformulated by Lev and Saphir (1945), in combination with Pernkopf and Wirtinger's ontogenetic theory, seems to have remained separate from this evolution.

What follows in this brief paper is subdivided into 3 parts: comments on (a) vectorial bulbus rotation as verified in recent studies; (b) the concept of a teratological series with special reference to the spectrum of transposition; (c) the significance of bulbar shrinkage.

(a) Vectorial bulbus rotation

This complex process may be conceived as the result of 3 components which occur more or less simultaneously (Fig.).

(i) Leftward shift of the bulbus *in toto* with concomitant enlargement of the metampulla (horizons XIII-XVIII, de Vries and Saunders, 1962; Asami, 1969) and with shrinkage of the bulbus and elongation of the truncus (horizons XVI-XVIII, Asami, 1969; Chuaqui and Bersch, 1972, 1973; horizons XVI-XIX according to Goor *et al.*, 1972).

(ii) Torsion of the bulbus at the bulbometampullar orifice through 45° clockwise rotation (looking downstream) (horizons XV-XVI, Asami, 1969).

(iii) Torsion of the truncus at the bulbotruncal orifice through 150° counterclockwise rotation (looking downstream) (horizons XV-XX, Asami, 1969; Chuaqui and Bersch, 1972, 1973; through 90-110° according to Goor *et al.*, 1972).

The sequence of these events is illustrated in Table 1. For the timing of ventricular septation (development of ventricular septum, truncus and bulbus septation, and closure of the interventricular foramen) see de Vries and Saunders (1962), Asami (1969), Goor *et al.* (1970), and Chuaqui and Bersch (1972, 1973). However, some discrepancies exist about the data presented in Table 1. Thus, for example, the ventricular septum is already present in horizon XIII according to Goor *et al.* (1970). Completion of the truncal septum is variously

Table 1 *Components of vectorial bulbus rotation and ventricular septation*

*Horizon** *Ovulation age (days)*	*XIII* *28*	*XIV* *29*	*XV* *31*	*XVI* *33*	*XVII* *35*	*XVIII* *37*	*XIX* *39*	*XX* *41*
Bulbus shifting	—	—	—	—	—	—		
Bulbus torsion			—	—				
Truncus torsion			—	—	—	—	—	—
Bulbar shrinkage				—	—	—		
Ventricular septum		—	—	—	—			
Truncus septum			—	—	—			
Fusion of bulbar ridges					—	—	—	
Closure of interventricular foramen						—	—	—

*After Streeter (1945, 1948, 1951).

Table 2 *Teratogenetic periods of main prototypes in transposition series*

*Horizon** *Ovulation age (days)*	*XIII* *28*	*XIV* *29*	*XV* *31*	*XVI* *33*	*XVII* *35*	*XVIII* *37*	*XIX* *39*	*XX* *41*
Cor bulboventriculare	—	—	—					
Beuren transposition			—	—				
Complete transposition			—	—				
Taussig-Bing anomaly				—	—			
Tetralogy of Fallot					—	—	—	
Eisenmenger complex					—	—	—	

*After Streeter (1945, 1948, 1951).

thought to occur at the following points: horizon XVI (Goor *et al.*, 1972; Anderson *et al.*, 1974b), horizon XVIII (Neill, 1956), horizon XIX (O'Rahilly, 1971); bulbar septation is completed in horizon XVII according to Anderson *et al.* (1974b).

Before bulbotruncal torsion the bulbar ridges run in a conspicuously twisted spiral, whereas at the truncus a straight septum develops. Torsion of the bulbotruncal orifice produces different effects on these septa: at the truncus it causes the primarily straight-structured septum to become helical, and at the bulbus it considerably reduces the extent to which the ridges spiral; torsion of the bulbometampullar orifice and bulbar shrinkage also contribute to this last effect (Fig.) (cf. Los, 1966, 1968; Chuaqui and Bersch, 1972, 1973; Goor *et al.*, 1972; Anderson *et al.*, 1974b).

(b) Concept of teratological series

This concept was introduced by Schwalbe (1906) and applied to cardiac teratology probably for the first time by Spitzer (1923). In the following brief account, previous ideas (Chuaqui, 1971) are elaborated, taking into account Bersch and Doerr's recent contribution (1976).

It is to Doerr's credit that he recognised in the apparently heterogeneous group of malformations known as Eisenmenger's complex, Fallot's tetralogy, the Taussig-Bing anomaly, and complete transposition, the existence of a teratological series (Doerr, 1951), and inferred from it the morphogenetic relation between these anomalies (Doerr, 1952).

A teratological series is a set of developmental anomalies that may be thought of as varieties of a similar basic morphological pattern. The members of such a series are thus related to one another in their visible form. However, the great heuristic value of this concept lies in the fact that these various entities may each represent distinct manifestations of a similar disturbance occurring at different times in development, in which case the members of the series are also morphogenetically linked. The series is then limited, on the one extreme, by the earliest, usually the most severe malformation, and on the other, by the last-occurring anomaly, representing the least deviation from normal. In the case of transposition, the morphogenetic accident involved is an arrest to a varying extent of vectorial bulbus rotation. The teratogenetic periods of some exemplars of this series are presented in Table 2 (cf Chuaqui and Bersch, 1972, 1973). Viewed the other way, analysis of the transposition series can serve to clarify the nature of a hypothetical, and complex, process of development, if this means that each member of the series has to be explained by a disturbance of that process. Such analysis then shows that the original series can be extended by additional entities which appear as transitional forms between the classical members (Chuaqui, 1969), for example, the cor bulboventriculare of Goor and Edwards (1972), equivalent to Goerttler's primitive laevocardia (1958, 1963, 1968), and Beuren's transposition (1960) (cf Chuaqui, 1969). This has happened more and more in recent years and the teratological series of transposition could now be described as a close-knit one in the sense that it is possible to conceive of a transitional anomaly between any two existing members. Thus, by the very recognition of the quasicontinuous nature of the series, one may infer that the underlying mechanism producing it ought to have the character of a biological continuum, as indeed a process of bulbus rotation has. This explains why it is impossible to categorise all its manifestations into a progression of well-defined, fixed entities; in systematisation one can only consider the intervals where well-recognised prototypes recur. Conventional distinctions seem of no decisive importance. In the Anglo-American papers concerning transposition and related lesions the expression *spectrum* or *continuous spectrum* of anomalies is used with a similar meaning to that of teratological series (Gessner, 1966; Gessner and Van Mierop, 1970; Lev *et al.*, 1972; Goor and Edwards, 1973; Anderson *et al.*, 1974a; Patterson *et al.*, 1974; Becker *et al.*, 1975; Rosenquist *et al.*, 1976).

From this approach it should not be concluded that the anomalous forms of the transposition series represent normal stages of cardiac development; processes of adaptation occur and there are likely to be other and different disturbances of vectorial bulbus rotation (cf Goerttler, 1963; Chuaqui and Bersch, 1973; Anderson *et al.*, 1974a), thus multiplying the possibilities.

(c) Comments on significance of bulbar retraction

Bulbar shrinkage is a proven fact which is particularly evident in horizon XVII (Asami, 1969; Goor *et al.*, 1972; Anderson *et al.*, 1974b). According to Goor *et al.* (1972) it begins after bulbar migration when half of the truncal torsion is completed. Nevertheless, as Chuaqui and Bersch (1973) point out, it is difficult to establish whether bulbar retraction merely accompanies vectorial bulbus rotation or is partly a cause of it. Anderson *et al.* (1974a, b) adopted the second alternative in considering it to be the cause of bulbar migration, and thus assigned to it a decisive role in the connection of the aorta to the future left ventricle. A failure of bulbar retraction would then imply, besides persistence of the bulbuauricular flange and a lack of mitral-aortic fibrous continuity, at least an overriding aorta. Until the case described by Bersch *et al.* (1975) it was impossible to know whether this introduction of an additional factor was correct or not, but here, as so often, teratology came to the rescue. These workers reported for the first time a malformation characterised by normally positioned great vessels, adult type morphology of the ventricles, except for a long muscular aortic conus measuring 4 cm, and absence of mitral-aortic fibrous continuity. Bulbar retraction, therefore, may be vital for the atrophy of the left portion of the bulboauricular flange and for the establishment of mitral-aortic fibrous continuity (cf Chuaqui and Bersch, 1973; Anderson *et al.*, 1974a, b), but this case shows that it is not a necessary condition for the connection of the aorta to the left ventricle.

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Gross distortion of atrioventricular and ventriculoarterial relations associated with left juxtaposition of atrial appendages

Bizarre form of atrioventricular criss-cross

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SUMMARY Two pathological specimens are described in which a bizarre distortion of atrioventricular and ventriculoarterial relations existed. In both cases anterior and leftward displacement of the tricuspid valve coexisted with rightward displacement of the infundibular regions and semilunar valves. Abnormal expansion of the AV canal, possibly secondary to malrotation of the cardiac tube, is considered as a possible cause of the anomaly.

One of the hearts showed severe subpulmonary stenosis produced by a valve-like structure which was well differentiated, with a complete annulus and chordae tendineae that inserted in a parachute-like fashion on the infundibular septum. The morphology of this structure was clearly different from that of the fibrous tags described in other anomalies. Its origin is uncertain.

These anomalies have important implications in relation to the nomenclature and classification of congenital heart malformations, and illustrate the value of recent modifications of the segmental approach.

The existence of hearts showing atrioventricular connections inappropriate to the relations of the atria and ventricles (for example, discordant atrioventricular connection in cases in which both morphologically right atrium and ventricle are placed to the right) was originally reported by Lev and Rowlatt (1961). Since then further reports of this anomaly have been published by Wagner *et al.* (1970), Van Praagh (1972), and Anderson *et al.* (1974a).

Such anomalies have interesting implications in relation to the nomenclature and classification of congenital heart malformations, which were reviewed by Anderson *et al.* (1974a). Their morphogenesis remains uncertain, but it has been suggested that these malformations result from abnormal rotation of the ventricular loop (Wagner *et al.*, 1970; Van Praagh, 1972). However the coexistence of other anomalies, which could be related to such malrotation, has not been adequately documented.

In this report we describe two hearts in which distortion of atrioventricular valve relations produced an effect similar to that reported in 'criss-cross' hearts. However, they also showed gross additional malformations which have not, to our knowledge, been previously reported and which have interesting morphogenetic implications.

Case reports

CASE 1

This man was 25 years old when seen for the first time at Clínica Puerta de Hierro (Madrid), and had been breathless and cyanosed from early infancy. On admission he was severely incapacitated.

On examination he was found to be deeply cyanosed, with clubbing. The liver was 4 cm below the costal margin. Slight cardiomegaly was present with a praecordial thrill. On auscultation, there was a pansystolic murmur (grade 5/6) in the third and fourth intercostal spaces to the left of the sternum, a third heart sound, and a diastolic filling murmur.

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The haematocrit was 65 per cent, haemoglobin 18 g/dl, and arterial oxygen saturation 58·5 per cent (breathing 100% oxygen). The electrocardiogram showed counterclockwise rotation of the QRS loop in the frontal plane with an axis of 90°, biatrial enlargement, and left ventricular epicardial patterns in all the praecordial leads. The chest *x*-ray film showed slight cardiomegaly with absence of the pulmonary arc and increased convexity of the lower left border of the heart; there was decreased pulmonary vascularity with signs of collateral circulation.

Angiocardiograms were interpreted as showing situs solitus and double inlet ventricle with double-outlet outlet chamber (aorta anterior and to the right of the pulmonary artery). There was left-sided juxtaposition of the atrial appendages and moderate regurgitation through the right atrioventricular valve. Severe subpulmonary stenosis was present.

In view of the hypoxaemia and the complexity of the case, an aortopulmonary shunt was attempted. The patient died in the postoperative period.

Necropsy showed visceroatrial situs solitus, with the cardiac apex pointing to the right (Fig. 1). There were two superior venae cavae of about the same size (the left one emptying into the coronary sinus). All the pulmonary veins drained into a cavity situated, for the most part, above and behind the right atrium, though it communicated only with the left atrium (thus resembling cor triatriatum). Left-sided juxtaposition of the atrial appendages was present. The left AV valve was morphologically mitral. It was placed in its normal position, being the most posterior of the 4 cardiac valves (Fig. 2a). The right AV valve was heavily calcified and displaced forwards compared with its normal position, lying on the anterior part of the floor of the right atrium (Fig. 2b), in front of the left AV valve; its morphology was atypical, having two leaflets and three groups of chordae tendineae which were inserted into the free wall of the main ventricular chamber and on to the borders of an anterosuperior outlet foramen (Fig. 3). Both AV valves opened into a large primitive ventricle which communicated with a small, right-sided outlet chamber through two defects. The outlet chamber was heavily trabeculated and gave rise to the aorta, while the pulmonary artery (placed just to the right of the right AV valve) was mainly arising above the septum.

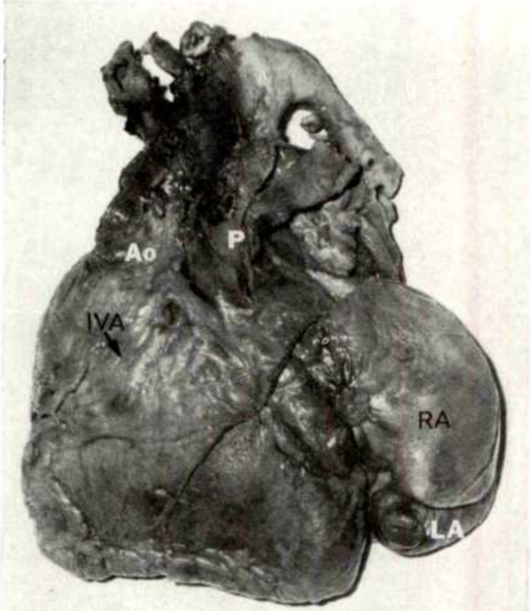
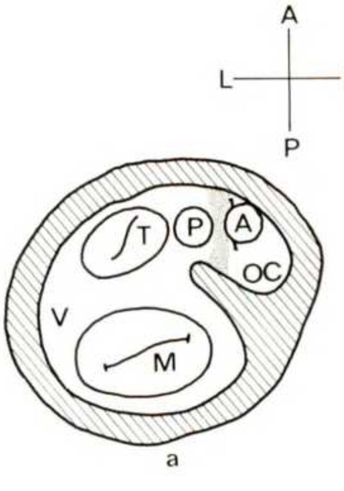


Fig. 1 *External view of the specimen of case 1, showing left-sided juxtaposition (RA, right atrial appendage; LA, left atrial appendage). The pulmonary trunk (P) origin is lower than the aortic (Ao). The descending or delimiting anterior artery is the boundary (IVA) between the outlet chamber and the primitive ventricle.*

The apical septal defect was situated in the trabeculated septum. The other defect was anterosuperior, produced by a malalignment between the infundibular septum (displaced to the right) and the other septal structures; its limits were the anterior wall of the ventricle, the muscular septum, the pulmonary outlet, and the right AV ring.

The pulmonary trunk had a diameter about three-quarters that of the aorta and straddled the septum, arising mainly from the outlet chamber, slightly behind and to the right of the right AV valve. The pulmonary valve was tricuspid and one of the leaflets was smaller than the other two. A raphe originated from one of the commissures and inserted in the wall of the pulmonary trunk.

There was another valve-like structure just below the pulmonary valve (Fig. 4). It was composed of tissue similar to the right AV valve with which it had fibrous continuity. It had three fibrous bands that had the appearance of fused commissures but which differed in position from the pulmonary commissures. There was an orifice of about 2 mm in the valve-like structure leading from the primitive ventricle to the pulmonary artery. Chordae tendineae arose from the leaflets of this valve and came together, like the strings of a parachute, in one main stem that inserted on the infundibular septum. This was the only structure producing stenosis in the subpulmonary tract.



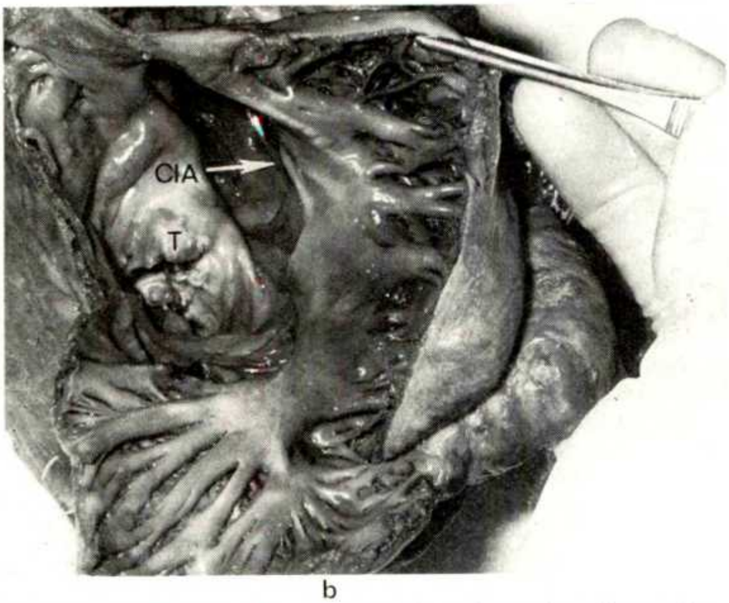


Fig. 2a *Case 1. Diagram to illustrate relation of ventricular chambers, atrioventricular valves, and semilunar valves. A, aorta; P, pulmonary artery; T, right AV valve; M, left AV valve; OC, outlet chamber; V, primitive ventricle.*
Fig. 2b *Case 1. Opened right atrial appendage shows the displacement of a heavily calcified right AV valve (T). Arrow points to the communication with the left atrium (CIA).*

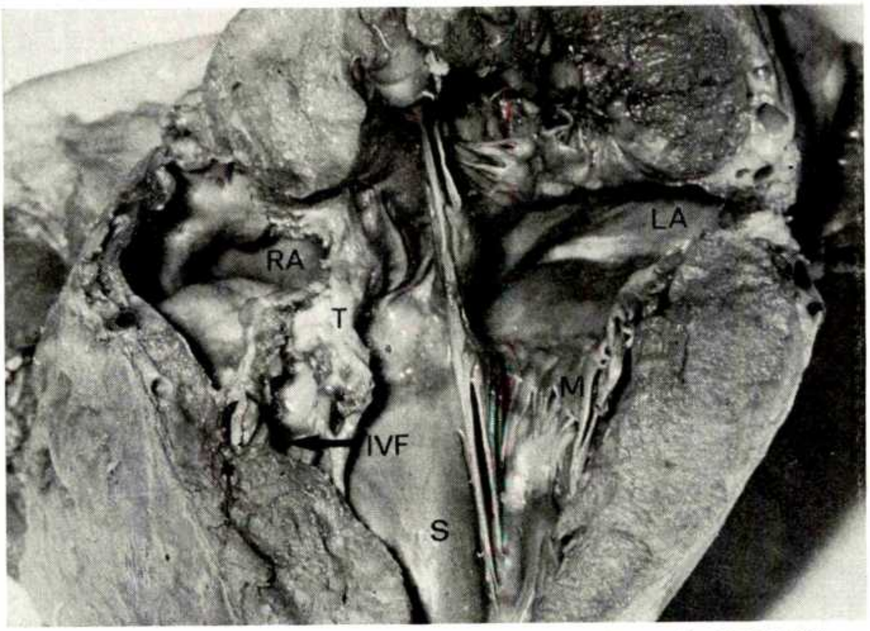
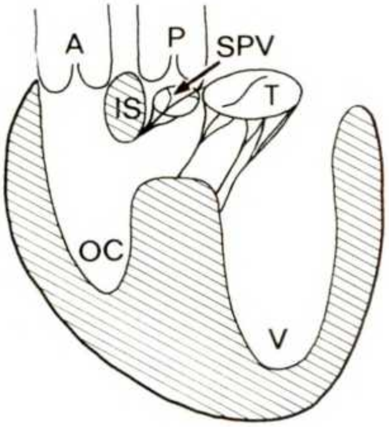
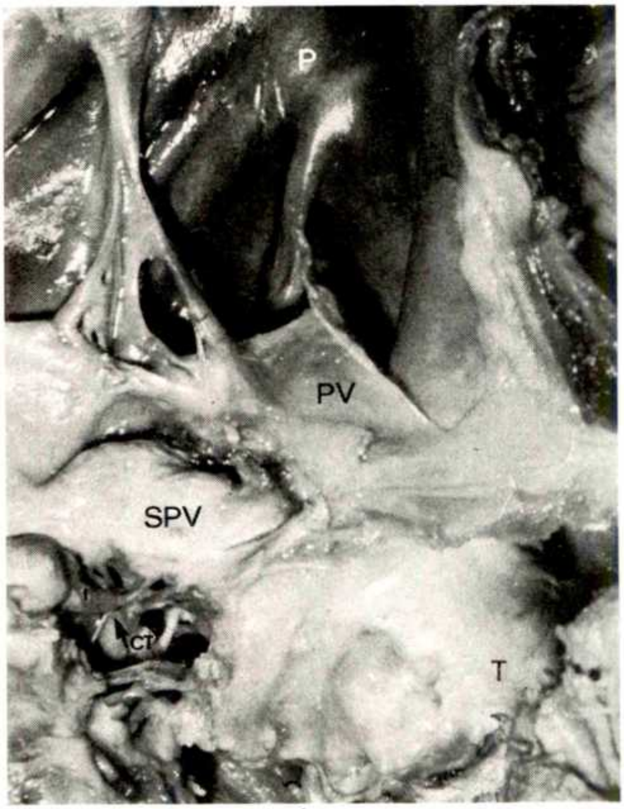


Fig. 3 *Case 1. Left ventricular septal aspect. Arrow points to the superior VSD (IVF). Right AV valve chordae tendineae are inserted upwards into the free ventricular wall, and downwards onto the septum; calcification of this valve is noteworthy. The mitral valve (M) is normal. S, septum; T, right AV valve; RA, right atrium; LA, left atrium.*



a



b

Fig. 4a *Case 1. Location and relations of the subpulmonary valve-like structure and the right AV valve. IS, infundibular septum.*

Fig. 4b *Case 1. Pulmonary outflow tract has been opened, showing the pulmonary valve (PV) and a subpulmonary valve-like structure (SPV), whose leaflets are in continuity with the right AV valve (T). Subpulmonary valve has been cut and arrow points to chordae tendineae (CT), arising like strings of a parachute from a main stem which passes rightwards, posterior, and inferior, and arises from the infundibular septum.*

CASE 2

This premature infant with a birthweight of 1·9 kg presented in the neonatal period with cyanosis and cardiac failure. Chest *x*-ray film showed dextrocardia in the presence of visceral situs solitus, and the electrocardiogram showed right atrial hypertrophy with P axis + 90° and QRS axis 0°. All praecordial leads showed qR complexes with tall R waves (30 mm). She deteriorated despite vigorous medical treatment and died before cardiac catheterisation and angiocardiography could be performed.

Necropsy showed atrial situs solitus, with the apex pointing to the right (Fig. 5). Left-sided juxtaposition of the atrial appendages was present. The right atrium received superior and inferior venae cavae and coronary sinus; a large secundum atrial septal defect was present. The left atrium received 4 pulmonary veins.

The right atrium was connected to an anterior ventricular chamber via a tricuspid valve which straddled the inflow septum by about 25 per cent, the septal cusp being attached to the crest of the septum. The inflow portion of the anterior ventricle lay on the left anterior shoulder of the ventricular mass. The trabeculated zone and outflow portion of the anterior ventricle lay on the right anterior shoulder of the ventricular mass, and both great arteries took origin from this ventricle, with a bilateral muscular infundibulum (Fig. 6). The tricuspid valve had septal, left, and right anterior cusps. In front of the latter was the ventriculo-infundibular fold separating it from the pulmonary valve. To the right of the pulmonary outflow tract was a well-formed infundibular septum with prominent septal and parietal extensions, which formed well-defined muscle bands around the

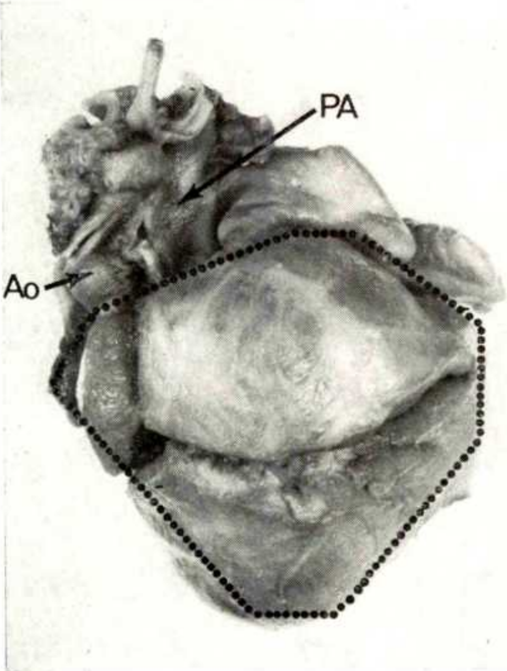


Fig. 5 *Anterior view of specimen from case 2 showing juxtaposed appendages. The transverse ventricular incision opens into the anterior morphological right ventricle. Dots delineate right ventricle.*

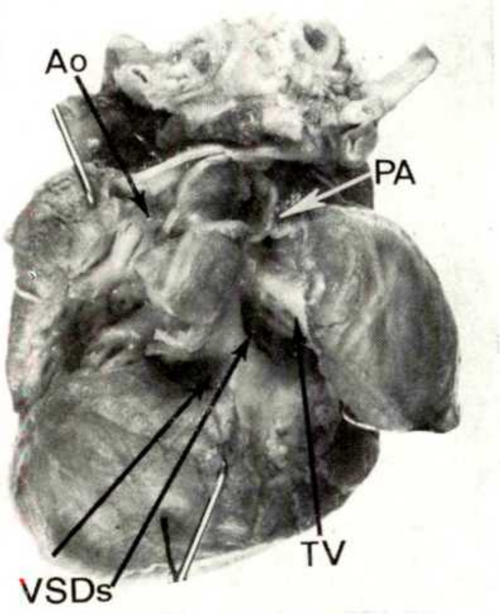


Fig. 6 *Case 2. Anterior view of right ventricle opened showing outflow tracts to aorta and pulmonary artery, tricuspid valve, and two ventricular septal defects.*

ventricular chamber, producing some obstruction to the aortic outflow tract. The latter lay further to the right and more posteriorly on the right shoulder of the ventricular mass and consisted of a trabecular zone with short infundibular segment. The aortic valve lay to the right of, and slightly posterior to, the pulmonary valve. There was a hypoplastic aortic arch and a persistent ductus arteriosus.

The left atrium connected with a posterior ventricle via a mitral valve (Fig. 7) and this ventricle formed the apex of the ventricular mass which was directed to the right. The posterior ventricle was a morphological left ventricle. The mitral valve was supported by multiple small papillary muscles on the parietal aspect (lying to the left). The septal cusp was orientated to the right and anteriorly. The posterior ventricle was connected to the anterior ventricle via two septal defects, the more leftward of which was an atrioventricular canal type of defect allowing some straddling of the tricuspid valve. The more rightward defect was a muscular defect which opened into the anterior ventricle just to the right of the infundibular septum and into the aortic outflow tract.

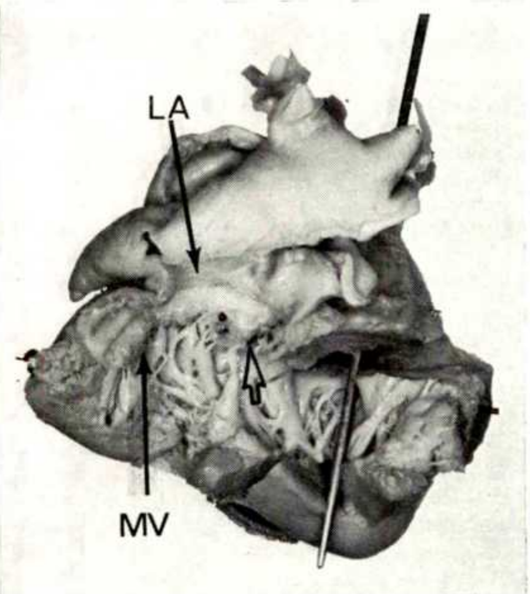


Fig. 7 *Case 2. Posterior view of heart with morphological left ventricle opened. Probe is passed through a ventricular septal defect into outflow tract of right ventricle. Open arrow pointing behind anterior leaflet of mitral valve indicates position of other ventricular septal defect.*

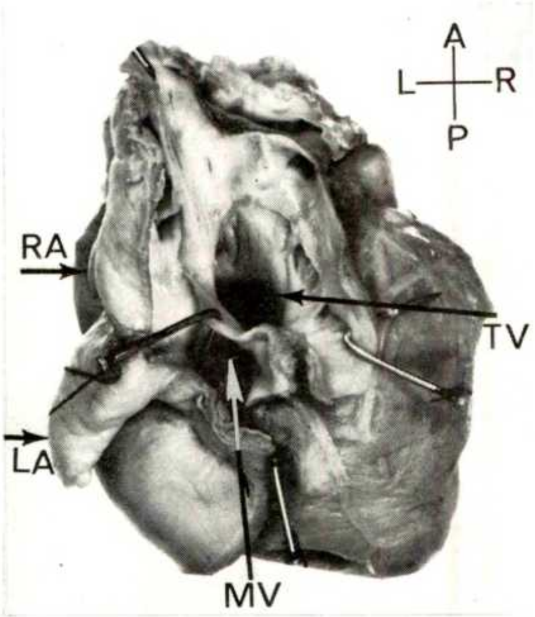


Fig. 8 *Case 2. Specimen viewed from above with atria opened, showing relation of tricuspid and mitral valves.*

The tricuspid valve lay more or less directly anterior to the mitral valve (Fig. 8, 9) and was directed anteriorly and to the left while the mitral valve was directed inferiorly and to the right. This produced a criss-cross effect involving the inflow areas of the ventricles, but the outflow tract of the anterior ventricle extending to the right tended to mask this effect.

Discussion

Both specimens showed striking morphological similarities which suggest similar pathogenetic mechanisms. Conspicuous distortion of AV valve relations was present in both hearts. Though its cause is uncertain, malrotation of the ventricular loop can be inferred from the presence of a right-sided apex and auricular juxtaposition.

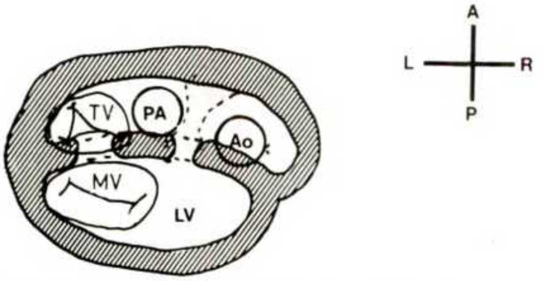


Fig. 9 *Case 2. Diagram to illustrate relation of ventricular chambers, atrioventricular valves, and semilunar valves. Infundibular septum indicated by light cross-hatching.*

The abnormal situation of the AV valves could be related to abnormal expansion of the AV canal. In normal cardiogenesis a number of morphogenetic movements, well described by Goor *et al.* (1972) and Anderson *et al.* (1974b), lead to a situation in which the posterior great artery is placed in front of and between both AV valves, with fibrous continuity among these structures. However, in our cases both great vessels remained to the right of the abnormally anterior right AV valve; this abnormal relation could explain the presence of double outlet right ventricle or outlet chamber in our cases (because the connection of any great artery to the left ventricle would be prevented by the mechanical obstacle of the right AV valve). The abnormal relations between the valves in these two cases do not occur during normal stages of cardiogenesis, and thus it seems likely that the abnormal location of the right AV valve (the most clearly pathologically situated in our cases) is a vital part of this anomaly. This abnormal location cannot be explained by a simple failure in rightwards expansion of the AV canal, and it is probable that an abnormally directed expansion took place. Whether this abnormal expansion is produced (or conditioned) by a primary anomaly of the AV canal, or is induced by other anomalies cannot be deduced with certainty, but this second possibility would be supported by the presence of other anomalies (of earlier genesis) suggestive of malrotation (right-sided apex, auricular juxtaposition).

The existence of fibrous structures ('fibrous tags') in the outflow tract of a ventricle or outlet chamber has been reported in association with several anomalies (mainly conotruncal malformations) (Levy *et al.*, 1963; Rastelli *et al.*, 1969; Riemenschneider *et al.*, 1969; Anderson *et al.*, 1975; Otero Coto *et al.*, 1978). It is unusual for such structures to produce significant obstruction. However, in our first case a valvular structure, supported by chordae tendineae arranged in a parachute fashion, with a small central opening, was present below the pulmonary valve, severely obstructing this outflow tract. This type of obstruction has not been previously reported to our knowledge. The origin of this structure is uncertain. It was not part of the right or left AV valves from which it was separated and had its own annulus just below the pulmonary valve. Nor does it seem to have been a derivative of the membranous septum, because the presence of double inlet ventricle argues against the existence of that structure and neither the location nor the morphology of the abnormal valve supports such a possibility. Its origin might be related to the differentiation of tissue derived from the cardiac jelly of Davis present in the bulbus and the bulboventricular junction, which has been said to be involved in the formation of part of the normal tricuspid valve (Ugarte *et al.*, 1976).

We have found incomplete absorption of the common pulmonary vein into the left atrium in several cases with a large left superior vena cava draining into the coronary sinus (Otero Coto, 1977). Thus we think that the abnormal morphology of non-restrictive cor triatriatum found in case 1 may be related to the presence of a large coronary sinus receiving a left superior vena cava. This fact could have interest in angiocardiographic evaluation of cases with this anomaly.

The existence of the reported anomalies has important implications in relation to the nomenclature of congenital heart disease. They offer, in our view, further evidence that any useful segmental approach must include both external relations between the segments and their connections. We believe that recent modifications (Otero Coto *et al.*, 1976; Otero Coto and Quero Jiménez, 1977; Shinebourne *et al.*, 1978) to the segmental approach of Van Praagh *et al.* (1964), whose initial limitations were recognised and largely overcome by Van Praagh himself in a later paper (1972), are a helpful advance in this field.

The authors gratefully acknowledge suggestions and criticisms of Dr Robert H. Anderson.

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Elective aortic and mitral valve surgery in patients over 70 years of age

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SUMMARY The results of elective cardiac surgery carried out between 1970 and 1975 on 29 patients over 70 years of age are reported. Operative mortality was 10 per cent, late cardiac mortality 14 per cent, with 72 per cent survival at a mean follow-up of 38·6 months. Before operation 96 per cent were in functional classes 3 and 4. After operation 90·5 per cent of late survivors were in functional classes 1 and 2 at a mean follow-up of 43·5 months. These results compare favourably with those in younger patients. Complication rate and length of hospital stay were unremarkable. The risks of neurological damage and of long-term anticoagulation are not increased. Emergency surgery carries a very high risk in this age group. The importance of biological youth and good left ventricular function is emphasised. For aortic stenosis at least prognosis is improved by surgery.

In 1973 the results of heart valve surgery at the National Heart Hospital in patients over 60 years of age were reported (Oh *et al.*, 1973). After these results an increased number of elderly patients have been referred for operation and in this report we have analysed the outcome of elective cardiopulmonary bypass surgery in patients over the age of 70.

Clinical material and methods

Between July 1970 and July 1975 29 patients over the age of 70 underwent open heart surgery at the National Heart Hospital and Harefield Hospital. The age range was 70 to 75 (mean 71) years. There were 20 men and 9 women. The NYHA classification of functional class (1964) was used to define effort tolerance. Before operation all except 1 patient were severely limited by cardiac symptoms to functional classes 3 or 4 (see Fig. A). All 29 patients were biologically young and though 16 patients had other medical conditions (see Table 1), these were not considered to contraindicate surgery.

Sixteen patients underwent preoperative left heart catheterisation, and in 4 this included selective coronary arteriography. Left ventricular end-diastolic pressures were recorded and ejection fractions were calculated by computerised analysis of end-diastolic and end-systolic frames of the left ventricu-

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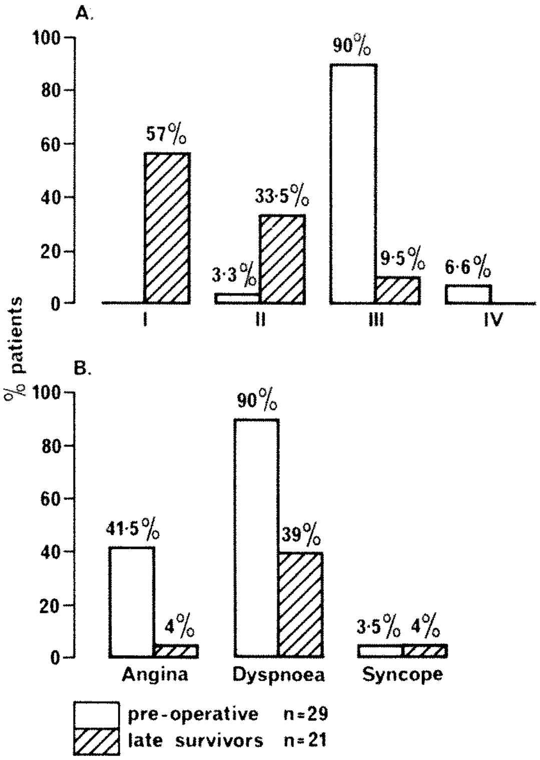

Fig. (*A*) *Functional class before and after surgery;* (*B*) *symptoms before and after surgery.*

Table 1 *Surgery in the over 70's*

Additional conditions present before surgery	*No. of patients*
Chronic airways obstruction	2
Gout	1
CVA (embolic from MVD)	1
Hypertension	2
Impaired cardiac conduction	2
Parkinson's disease	1
Chronic DU	1
Vertebro-basilar insufficiency	1
Diabetes mellitus	1
Intermittent claudication	1
Hashimoto's disease	1
Prostatism	2

CVA = cerebrovascular accident; MVD = mitral valve disease; DU = duodenal ulcer.

lar angiogram. Only normally conducted beats were analysed; post-ectopic beats were excluded.

Operative mortality was defined as death at operation or from complications before discharge. Early survivors were those who left hospital alive after operation. Late survivors were those who were alive at the final follow-up.

All patients were seen at either the National Heart Hospital or at Harefield Hospital within 1 year and in many instances more recent information was obtained from their general practitioners.

Results

Preoperative diagnoses and the operations performed are shown in Table 2. Bypass times were recorded for 17 out of 29 operations and the duration of myocardial ischaemia from aortic clamping was recorded in 6. The bypass time varied from 33 to 136 minutes, with a mean of 64 minutes. Ischaemic time varied from 10 to 40 minutes, with a mean of 26 minutes. With 1 exception all patients whose ischaemic time exceeded 10 minutes were operated on before 1973.

LEFT VENTRICULAR FUNCTION

The left ventricular end-diastolic pressure (LVEDP) varied from 8 to 30 mmHg, with a mean of 16 mmHg. Left ventricular ejection fractions ranged from 0·40 to 0·86, with a mean of 0·58. There was no obvious correlation between LVEDP and ejection fraction, and ejection fractions were well maintained despite raised end-diastolic left ventricular pressures.

OPERATIVE MORTALITY

Of the 29 patients, 3 died in hospital after operation giving an operative mortality of 10 per cent: 1 at 5 days after resection of infarcted ileum and decompression colostomy, another at 11 days from pneumonia after prolonged ventilation, and the third at 17 days from diabetic ketoacidosis complicated by septicaemia and renal failure after an initially excellent haemodynamic recovery. One of these deaths occurred after aortic valve replacement and 2 after mitral valve replacement.

POSTOPERATIVE COURSE

Sixteen patients (55%) had an uncomplicated postoperative course. In the remaining 13 patients (45%) 24 complications occurred (Table 3). Apart from those associated with the operative mortality these were minor. Only 1 patient suffered intellectual impairment and/or personality change after cardiopulmonary bypass. This consisted of impairment of short-term memory with associated depression and followed aortic valve replacement with a bypass time of 50 minutes. There were no focal neurological lesions.

The average postoperative hospital stay was 19 days (range 11 to 35). Of 26 survivors, 9 (34%) were discharged home within 14 days of operation.

LATE DEATHS

There were 5 late deaths, 4 cardiac and 1 resulting from other causes, giving a late cardiac mortality of 13·8 per cent and a late non-cardiac mortality of 3·4

Table 2 *Preoperative diagnoses and operative treatment*

No. of patients	*Diagnosis*	*Operations*	
16	Calcific aortic stenosis*	Aortic valve replacement × 18	9 Starr-Edwards 8 Homograft 1 Björk-Shiley
2	Aortic regurgitation		
1	Aortic regurgitation after previous aortic dissection	Resuspension of aortic valve and dacron replacement of ascending aorta	
1	Aortic and mitral stenosis	Aortic valve replacement and mitral valvotomy × 2	1 Starr-Edwards 1 Björk-Shiley
1	Mixed aortic valve disease and mitral stenosis		
4	Mitral regurgitation	Mitral valve repair × 1	
3	Mixed mitral valve disease	Mitral valve replacement × 6	3 Starr-Edwards 2 Inverted homografts 1 Braunwald-Cutter
		2 additional tricuspid annuloplasties	
1	Mitral stenosis	Mitral valvotomy	

*The mean aortic valve gradient in 12 patients who were investigated was 90 mmHg, with a range of 50 to 130 mmHg.

Table 3 *Surgery in over 70's*

Postoperative complications	*No. of patients having each complication*
Atrial fibrillation	5
Temporary pacing	4
Ventricular tachycardia Ventricular fibrillation	1
Pulmonary collapse	5
Pneumonia†	2
Pneumothorax	1
Ventilatory failure†	1
Reoperation for haemorrhage	1
Diabetic coma†	1
Transient confusional state	1
Small bowel infarction†	1
Septicaemia and renal failure†	1
Total complications	24

†Signifies major causes of death.
9 of these complications occurred in 2 patients who were hospital deaths.
16 out of 29 patients had an entirely uncomplicated postoperative course.

per cent. The postoperative survival in the 5 who died varied from 3 to 27 months, mean 19 months, while that of the late survivors ranged from 20 to 80 months, mean 43·5 months. Mean survival for all operative survivors was 38·6 months. Of 4 patients who died from cardiac causes during follow-up, 3 benefited initially from their operation. One patient was active and asymptomatic after homograft aortic valve replacement until he died suddenly with chest pain 21 months after operation. Another patient improved from class 3 to class 2 for 1 year after aortic valve replacement, then he deteriorated and died 27 months after operation from progressive impairment of left ventricular function. The third patient improved from class 3 to class 2 for 6 months before developing mitral regurgitation around his Starr-Edwards prosthesis which caused severe haemolytic anaemia (haemoglobin 8·0 g). He was not referred back to the National Heart Hospital and died of pneumonia at 21 months. One patient who had severe preoperative impairment of left ventricular function derived no benefit from mitral valve replacement and died 12 months after operation. The other death occurred in a patient who had already improved from class 3 to class 2 and had significant reduction in heart size before her death 3 months after Starr-Edwards aortic valve replacement and mitral valvotomy. The cause of death is unknown.

CHANGES IN EFFORT TOLERANCE AND SYMPTOMS

The change in symptoms and functional class after operation in the 21 late survivors at a mean follow-up time of 43·5 months is shown in Fig. A and B.

Before operation all patients except 1 were so severely incapacitated by either angina or effort dyspnoea or a combination of the two, that 96 per cent were in functional class 3 or 4 (Fig. A). The exception was a man with severe aortic regurgitation from a previous aortic dissection who had minimal symptoms (functional class 2). Of the 21 late survivors at a mean follow-up time of 43·5 months, 12 (57%) were in functional class 1 and 7 (33·5%) in class 2. Only 2 patients (9·5%) were in class 3. One had been in class 4 before operation, the other initially improved to class 1 but later deteriorated because of effort dyspnoea and intermittent claudication, which was a new symptom.

Comparison of pre- and postoperative symptoms shows a similar improvement. The reduction of angina from 41·5 to 4 per cent was entirely the result of relief of severe aortic stenosis. No patient who underwent aortic valve replacement had additional coronary bypass grafts. At first sight the reduction in the incidence of dyspnoea from 90 per cent to 39 per cent was less dramatic. However, among those patients who had residual dyspnoea 75 per cent were in functional class 2 while before operation 88 per cent had been in class 3 or 4. The single late survivor with syncope developed Adams-Stokes attacks caused by complete heart block 32 months after aortic valve replacement for calcific aortic stenosis. Since implantation of a permanent pacemaker there have been no further attacks.

HEART FAILURE AND MAINTENANCE THERAPY

Only 1 of 21 late survivors showed evidence of heart failure whereas preoperatively 23 out of 29 patients had clinical and radiological evidence of failure. No antifailure therapy was required for 9 of the 21 late survivors, 4 were taking digoxin, 1 diuretics, and only 6 required a combination of both digoxin and diuretics.

Sixteen patients had valve replacement with a mechanical prosthesis and required long term anticoagulation. During a follow-up ranging from 3 to 80 months (mean 38·6 months), there were no complications from anticoagulation treatment and no embolic events. None of these patients was significantly hypertensive before or after operation.

Discussion

The life expectancy for healthy 70-year-old men and women has recently been quoted as 10 and 12 years, respectively (*British Medical Journal*, 1976). Reviewing the 'natural history' of patients of all age groups who died from aortic stenosis, Ross and Braunwald (1968) found the mean survival after the onset of symptoms was 3 years, 80 per cent of deaths occurring within 4 years. Similar observations were made by Frank and Ross (1967), who found an 83 per cent mortality in 5 years in a prospective study of 12 patients treated medically after investigation had shown an aortic valve gradient of at least 50 mmHg. Thus symptomatic aortic valve disease may severely curtail life expectancy in otherwise fit 70-year-old patients. In this series survival for patients with aortic stenosis was 86 per cent (14/16), at a mean follow-up time of 43·5 months. Thus the prognosis of this condition is improved by surgery even in this age group.

The overall results of this series (hospital mortality 10% and late cardiac mortality 14% with a mean follow up period of 41 months) were similar to those of Oh *et al.* (1973) (18% and 11% in 20 months, respectively), even though their patients were younger (85 [74·5%] between 60 and 64 years and only 2 [1·8%] over 70), and less severely disabled before operation (50% in class 1 or 2 as compared with 93% in class 3 or 4). The probable reasons for this improvement are in part advances in cardiac surgery and postoperative care and in part stricter selection in terms of biological age and preoperative ventricular function.

Previous reports of cardiac surgery in the elderly have either dated from the early days of open heart surgery or dealt mainly with patients less than 70 years of age or have had only short periods of follow-up. These include: Austen *et al.* (1970) for aortic valve disease, Guthrie *et al.* (1972) for valve disease, Barnhorst *et al.* (1974) and Quinlan *et al.* (1975) for valve disease and coronary artery surgery, and Asho *et al.* (1973) and Meyer *et al.* (1975) predominantly for coronary artery surgery. These series are summarised in Table 4. The higher operative mortality reported by Austen *et al.* (1970) and Guthrie *et al.* (1972) probably reflects the early date of these 2 reports. Our operative mortality of 10 per cent was similar to that of the other series which varied from 9 to 15·7 per cent (see Table 4).

Isolated aortic valve replacement carried the lowest operative risk for all patients undergoing valve replacement. The mortality was 5·3 per cent in the present series, 10·6 per cent from Barnhorst *et al.* (1974), and 16 per cent from Quinlan *et al.* (1975). Mitral valve replacement carried a higher risk which varied from a mortality of 9 per cent (Quinlan *et al.*, 1975) to 20 per cent (Barnhorst *et al.*, 1974) and 25 per cent in the present series. For coronary artery surgery alone operative mortalities of 9 per cent and 12 per cent were reported for the larger series by Ashor *et al.* (1973) and Meyer *et al.* (1975), while Quinlan *et al.* (1975) and Barnhorst *et al.* (1974) reported no mortality in 12 patients and 3·7 per cent in 27 patients.

Only Quinlan *et al.* (1975) gave results of emergency surgery in elderly patients. This was defined as surgery which had to be carried out within 24 hours of the initial assessment of the patient. In a mixed group of 20 patients whose emergency operations included aortic valve replacement (7), coronary bypass grafts (4), resection of left ventricu-

Table 4 *Synopsis of comparable quoted series*

Author and centre and period of series	*No. of patients*	*Age-range and mean*	*Operative mortality*	*Follow-up period*	*Late mortality*	*Functional class*	
						Pre-operative	*Post-operative*
Austen *et al.* (1970) Massachusetts General Hospital, Boston 1961-69	40	70-85 $\bar{x}$ 74·6	20%	Mean 28/12	7·5%	20%-III 80%-IV	'All survivors greatly improved'
Guthrie *et al.* (1972) St. Mary's Long Beach Hospital, California 1964-71	36	65-75 $\bar{x}$ 68	39%	Mean 31/12	3%	52%-III 48%-IV	$100\% \left\{ \begin{array}{l} \text{I} \\ \text{II} \end{array} \right.$
*Ashor *et al.* (1973) Good Samaritan Medical Center, Los Angeles 1969-72	100	$\bar{x}$ 67·8	6%	Mean 11/12	4%	—	—
Barnhorst *et al.* (1974) Mayo Clinic, Rochester 1968-73	300	66-80 (91 over 71)	15·7%	—	—	76%-III 20%-IV	— —
*Meyer *et al.* (1975) St. Luke's Episcopal Hospital, Houston, Texas 1969-74	75	70-79 $\bar{x}$ 71·9	22·1%	—	—	—	—
Quinlan *et al.* (1975) Peter Bent Brigham Hospital, Boston 1970-74	74	65-82 $\bar{x}$ 70	11%	4-48/12	7·5%	61%-III 37%-IV	75%-I 21%-II
(1977) National Heart Hospital, London 1970-75	29	70-75 $\bar{x}$ 71	10%	Mean 38·6/12	14%	90%-III 6·6%-IV	57%-I 33·5%-II

Predominantly coronary artery surgery.

lar aneurysm (4), and acute aortic dissection (4), the mortality was 40 per cent.

Although not included in this report 8 patients over 70 underwent emergency surgery at Harefield Hospital during the period under review with an operative mortality of 75 per cent. These patients were critically ill with severe lesions. Two had mitral valve disease (1 with active endocarditis), 1 had critical aortic stenosis, 2 had postinfarction ventricular septal defects (1 survivor), 2 had acute aortic dissection (1 survivor), and 1 had coronary disease and mitral regurgitation with severe angina and left ventricular failure. These results emphasise the comments of Quinlan *et al.* (1975) on the importance of avoiding emergency cardiac surgery in patients over 70 whenever possible.

The question of the place of additional coronary bypass surgery in elderly patients undergoing valve replacement remains unsolved. Barnhorst *et al.* (1974) found that the mortality of patients undergoing aortic valve surgery and coronary bypass surgery was twice that of aortic valve replacement alone, being 22 per cent compared with 10·6 per cent. Similarly, Meyer *et al.* (1975) found a 30 per cent mortality in 21 patients undergoing coronary bypass surgery and valve replacement (19 aortic and 2 mitral), but Quinlan *et al.* (1975) attributed 8 of 16 hospital deaths to unoperated coronary disease. In the series reported here 18 patients underwent aortic replacement alone, with a mortality of 5·3 per cent. Though the coronary circulation of these patients was not assessed we agree with Barnhorst *et al.* (1974) that it has yet to be shown that additional coronary surgery in elderly patients will reduce operative mortality or prolong survival.

Neurological damage from cardiopulmonary bypass does not appear to be a major hazard in this age group. Quinlan *et al.* (1975) reported 1 patient who had a hemiplegia after femoro-femoral bypass for a thoracic aortic aneurysm and we report 1 patient with persistent impairment of short-term memory and associated depression after uncomplicated aortic valve replacement. Postoperative confusional states were not common or persistent. The incidence of late emboli was low. The report from the Mayo Clinic (Barnhorst *et al.*, 1974) was exceptional in that 4 deaths in 300 patients were the result of cerebrovascular complications and a high incidence of additional unspecified 'cerebrovascular complications' was noted. In no series did long-term anticoagulation produce problems, with the possible exception of 1 patient who died from a subdural haematoma after an accidental fall (Austen *et al.*, 1970).

Elective cardiac surgery in patients over 70 is only justified if it can be shown to reduce disabling symptoms or to increase life expectancy. In this report 81 per cent of operative survivors were alive at a mean follow-up period of 38·6 months. Before operation 96 per cent were limited by cardiac symptoms to functional class 3 or 4. Of late survivors 90·5 per cent were in functional class 1 or 2; 43 per cent did not require any antifailure therapy, and only 29 per cent required both digoxin and diuretics. In many patients this improvement represented the difference between dependence and independence. The report shows that the results of elective cardiac surgery in severely disabled patients over the age of 70 who are biologically young and have good left ventricular function are comparable to those for patients over 60. The increased risk of emergency cardiac surgery in patients over 70 is emphasised.

We thank our colleagues at this and other hospitals for permission to include their patients.

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Angiosarcoma of the heart

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SUMMARY Two cases of angiosarcoma of the heart are described. In one the tumour, which arose from the right atrium, was demonstrated during life by angiography. In the other, diagnosed only at necropsy, the tumour arose from the right ventricle. Both cases illustrate many of the typical features of this rare tumour and the difficulties of antemortem diagnosis.

Primary tumours of the heart are rare. Straus and Merliss (1945), in a review of 480 331 necropsies, found the incidence of primary cardiac tumour to be 0·0017 per cent. Angiosarcoma is among the least common. It usually arises from the right atrium and only rarely from the pericardium, right ventricle, or left atrium.

Case reports

CASE 1

A 42-year-old man was admitted in July 1976 complaining of severe lumbar and epigastric pain. He had first developed lumbar pain after a fall 2 years previously, but it had become more severe in the 6 months before admission. In March 1976 he had been admitted to the orthopaedic department of another hospital complaining of lumbar and epigastric pain, malaise, and weight loss. During that admission he was found to be anaemic, but no definite diagnosis was made and he was discharged on oral iron and indomethacin. There was no history of contact with vinyl chloride.

On examination he had a low grade pyrexia, intermittent mental confusion, and mild tachypnoea. The jugular venous pressure was raised 3 cm and he was in sinus rhythm at 70 to 110/min. The blood pressure was 90/50 mmHg without paradox. A pericardial friction rub was audible throughout the praecordium. The electrocardiogram was normal and the chest *x*-ray film showed globular cardiac enlargement with normal lung fields. The haemoglobin was 12·1 g/dl with normal indices, the white cell count 13·3 × 10^9/l with 70 per cent neutrophils, and the erythrocyte sedimentation rate was 77 mm/hour. A Mantoux test and investigations for collagen disease were negative. *X*-ray film of the lumbar spine showed mild degenerative changes only. M-mode echocardiography confirmed the clinical impression of a pericardial effusion.

Six days after admission cardiac tamponade developed. Twenty-five ml blood-stained pericardial fluid were aspirated, with relief of the tamponade. Malignant cells were not seen on cytological examination of the aspirate. One month after admission open pericardial biopsy was carried out through a left thoracotomy. No tumour was seen. The biopsy showed a grossly thickened pericardium with extensive fibroblastic proliferation and focal aggregates of lymphocytes, but no evidence of malignancy.

The jugular venous pressure returned to normal after pericardial biopsy, and remained so during the rest of his illness. However, the patient continued to deteriorate. In October 1976 a bone scan showed patchy loss of uptake in the lumbar region and malignant cells were found on bone marrow aspiration. The patient developed a sinus tachycardia with a gallop at this time, and the electrocardiogram showed nonspecific ST and T wave abnormalities, though the chest *x*-ray film showed a normal cardiac silhouette. His condition deteriorated further and he died in December 1976.

At necropsy the main tumour was in the anterior part of the right ventricle, measuring 5 × 4 × 4 cm and infiltrating the full thickness of the myocardium and endocardium. The pericardium was firmly adherent to the heart and contained numerous haemorrhagic metastases on the outer surface. There was confluent subpericardial tumour, approximately 0·5 cm thick, surrounding the whole heart. There was also a large number of haemorrhagic metastases in the lungs, liver, spleen, and lumbar

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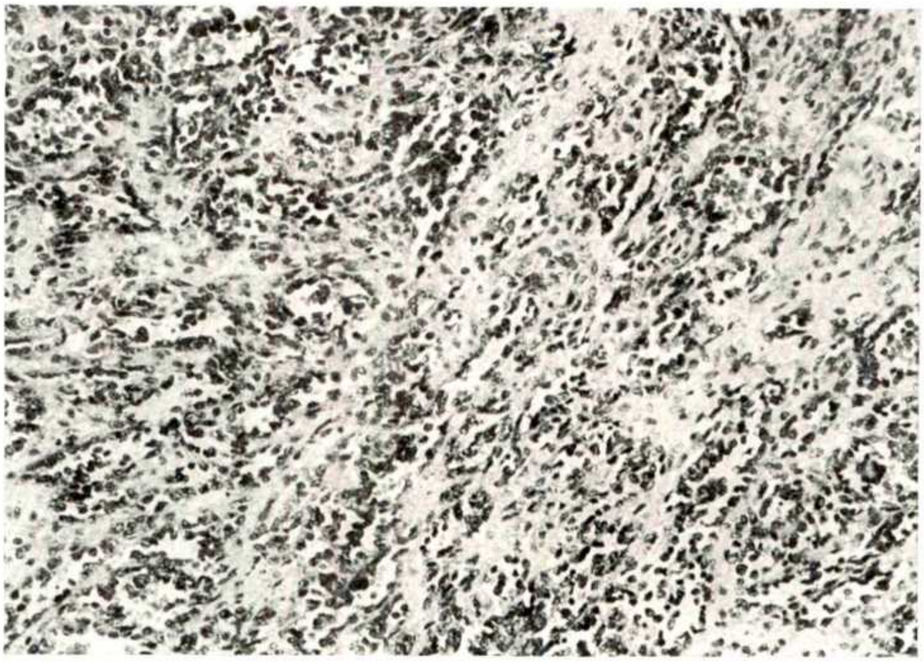

Fig. 1 *Photomicrograph of a solid part of the tumour from the right ventricle showing a pleomorphic, spindle-cell pattern, with numerous capillary sized vascular spaces.* (*H and E.* × *150.*)

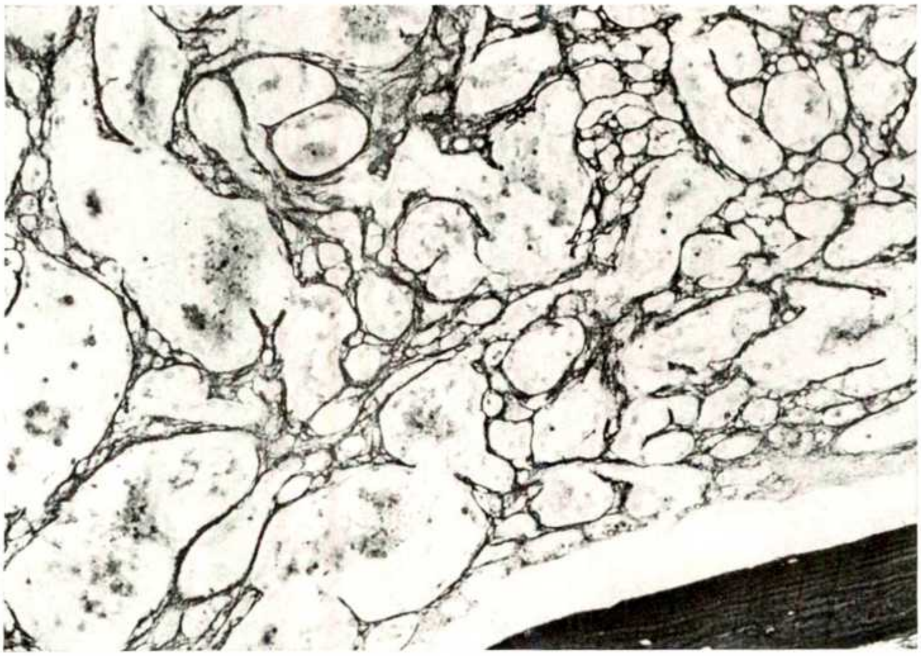

Fig. 2 *Vertebral metastasis showing the vasoproliferative nature of the tumour and outlining the vascular spaces.* (*Reticulin.* × *150.*)

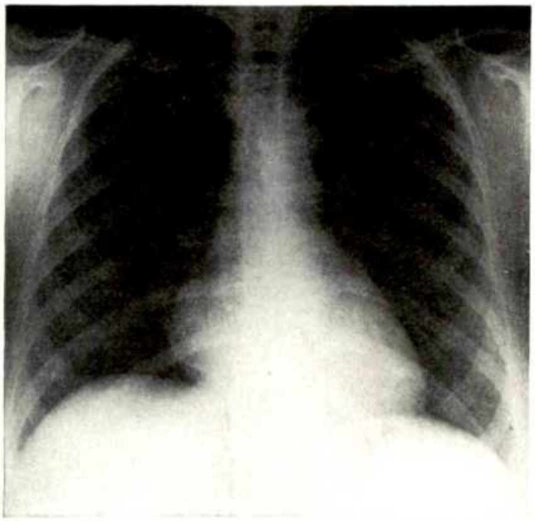

Fig. 3 *Chest* x-*ray film (case 2) showing a bulge on the right border of the heart.*

vertebrae. The histological appearance of the tumour in the pericardial space was that of a solid spindle-cell sarcoma, but in other sites, such as the liver and right ventricular wall, there were large vascular spaces in the tumour itself. In the vertebrae the tumour had definite vasoformative properties.

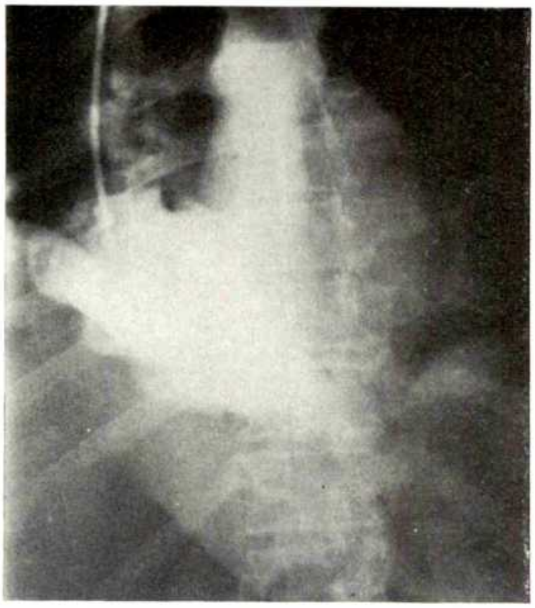

Fig. 4 *Angiogram (case 2) after right atrial injection, showing an apparent outpouching of the right atrium.*

The overall appearances were those of angiosarcoma (Fig. 1 and 2).

CASE 2

A 48-year-old woman underwent subtotal thyroidectomy for a multinodular goitre with substernal extension in January 1977. The histology was of a benign nodular colloid goitre. Her only symptom after operation was nonspecific chest pain. But whereas before operation the chest *x*-ray film had been normal, afterwards it showed gross cardiac enlargement. There were no abnormal physical signs but the electrocardiogram showed generalised flattening of the T waves and frequent ventricular ectopic beats. M-mode echocardiography showed a large pericardial effusion. The haemoglobin was 10·3 g/dl with a normal blood film and the erythrocyte sedimentation rate was 50 mm/hour. Antinuclear factor, autoantibodies, and Mantoux test were negative, and a diagnosis of viral or idiopathic pericarditis was made.

One week later a pericardial friction rub was heard. The effusion cleared spontaneously, confirmed by echocardiography, with conservative management only and the patient was discharged 3 weeks after admission for subtotal thyroidectomy.

Chest pain and malaise continued after discharge and treatment with tetracosactrin zinc 0·5 mg twice weekly was started 2 months later. This was changed to prednisolone 40 mg daily after one week, when she was readmitted. The chest *x*-ray film now showed a bulge on the right border of the heart (Fig. 3). Right atrial angiography showed an apparent outpouching of the right atrium (Fig. 4). She was discharged again after 3 weeks, on prednisolone, but continued to complain of nonspecific pain in the chest and arms, together with weight gain and shortness of breath. She was admitted on 2 further occasions with an increase in the jugular venous pressure and sinus tachycardia, but at no stage was there clinical or echocardiographic evidence of reaccumulation of pericardial fluid.

At the end of June 1977, because of her unexplained deterioration, cardiac catheterisation was repeated. Right atrial angiography now showed a mass about 2 cm in diameter, projecting into the right atrium. A left ventricular injection showed an abnormally contracting left ventricle, its anterior surface, from the aortic root to the apex, being almost completely akinetic. Injection into the left coronary artery was followed by a blush over the whole of the base of the heart, and injection into the right coronary artery showed the proximal part of the vessel to be displaced around a non-opacified area. After arterial clearing there was again a blush in the

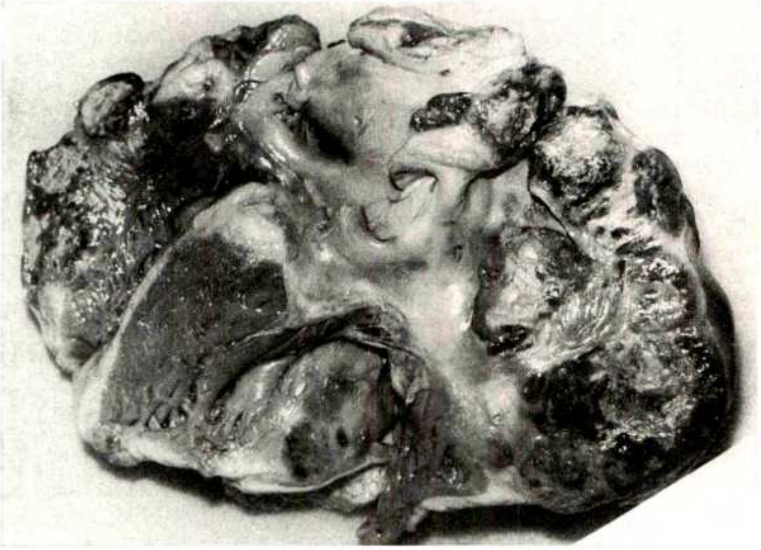

Fig. 5 *Opened heart (case 2) showing the main mass of tumour infiltrating the right atrial wall, with intracavitary extension. Multiple smaller nodules of tumour are visible on the cut surface of the interatrial septum and left ventricle, and an epicardial tumour nodule is on the upper part of the interventricular septum.*

region between the right coronary artery and the right border of the heart. The appearances were those of a tumour of the right atrium with involvement of the base of the heart.

Subsequent chest *x*-ray films suggested secondary deposits in the lungs. Needle biopsy of the lung was attempted in order to make a histological diagnosis, but no tumour was obtained. The patient died the next day.

At necropsy the heart weighed 1300 g. There were

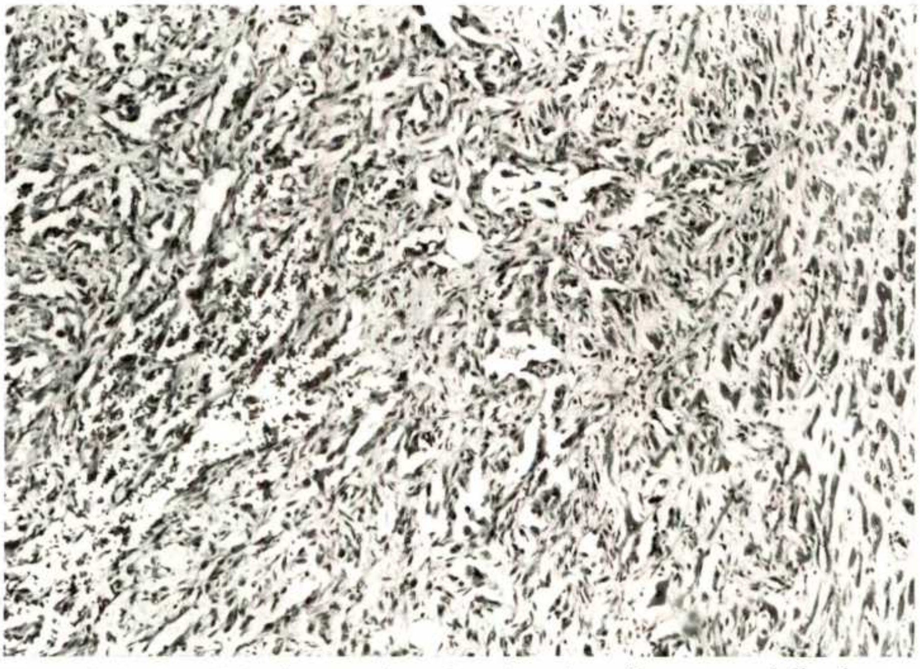

Fig. 6 *Section (case 2) showing a vascular and vasoformative malignant tumour infiltrating myocardium on the right. (H. and E. × 90.)*

multiple haemorrhagic tumour nodules, from 1 to 5 cm in diameter, scattered over the entire epicardial surface. The tumour appeared to be originating from the right atrium where there was an intracavitary extension, approximately 4 cm in diameter, reducing the cavity (Fig. 5). There were multiple pericardial adhesions to the surface over epicardial nodules. Metastases were present in brain, lungs, liver, and ovaries, mainly 0·5 to 2 cm in diameter. The histology was that of angiosarcoma (Fig. 6).

Discussion

The constancy of symptoms and physical signs in patients with angiosarcoma of the heart has been stressed by many authors (McNalley *et al.*, 1963; Glancy *et al.*, 1968; Hollingsworth and Sturgill, 1969). The most frequent symptoms are general malaise, chest pain, fever, and haemoptysis, and the physical signs include a pericardial friction rub and raised jugular venous pressure. The chest *x*-ray film may show cardiomegaly, sometimes with a bulge on the right border of the heart. The electrocardiogram may be normal at the time of presentation or show nonspecific ST and T wave abnormalities. Echocardiography may confirm a pericardial effusion, which typically is blood-stained on aspiration. Ports *et al.* in 1977 described 4 cases of right ventricular tumour, 3 myxomas, and 1 metastatic melanoma, in which the tumour was seen on M-mode echocardiography. In 2 cases the site of attachment of the tumour was shown by two-dimensional echocardiography.

The prognosis is poor, with few patients surviving more than a few months from presentation.

At necropsy there is obliteration of the pericardial sac by tumour and often pulmonary and rib metastases. Though it is often difficult in the presence of extensive infiltration of surrounding structures by the tumour to determine the precise site or origin, it usually appears to arise from the right atrium. Other sites are much less common.

We have found 15 cases reported in which the probable or possible site of origin was the pericardium (Glancy *et al.*, 1968; Hollingsworth and Sturgill, 1969; Hansson *et al.*, 1970; Poole-Wilson *et al.*, 1976), 6 in which it was the right ventricle (Lange and Christiansen, 1947; Amsterdam *et al.*, 1949; Tatsumi *et al.*, 1949; Glassy and Massey, 1950; Groom, 1956; Thompson *et al.*, 1977), and 2 in which it was the left atrium (Gross and Englehart, 1937; Hager *et al.*, 1970).

Few cases of angiosarcoma of the heart have been diagnosed in life. In a review of the published reports in 1968, Glancy *et al.* found, out of 41 cases of angiosarcoma of the heart, 12 in which the diagnosis had been suspected clinically and only 7 in which it was confirmed before death. We have found a further 8 cases in which the diagnosis was made before death (Allaire *et al.*, 1964; Hollingsworth and Sturgill, 1969; Hager *et al.*, 1970; Laws *et al.*, 1973; Poole-Wilson *et al.*, 1976; Rossi *et al.*, 1976; Thompson *et al.*, 1977).

In the 7 cases cited by Glancy *et al.* the diagnosis was made by biopsy of the tumour or its secondary deposits in 4, by demonstrating tumour cells in the pericardial fluid in 2, and the diagnosis was suspected at right heart angiography in 1, though not confirmed histologically during life. In the 8 other cases we have found, the diagnosis was made at thoracotomy in 6 cases (Allaire *et al.*, 1964; Hollingsworth and Sturgill, 1969; Hager *et al.*, 1970; Laws *et al.*, 1973: cases 1 and 4; Poole-Wilson *et al.*, 1976) and by angiocardiography followed by thoracotomy in 2 (Rossi *et al.*, 1976; Thompson *et al.*, 1977).

Despite the fact that we suspected malignancy from an early stage in our first case, we were unable to confirm this until a bone-marrow aspiration 10 weeks after initial admission, and in spite of cytological examination of the pericardial fluid and open pericardial biopsy. It was particularly unusual to fail to make the diagnosis at open exploration of the pericardium, especially as this was carried out at a time when the disease must have been far advanced. The histological diagnosis of angiosarcoma of the heart was only made at necropsy. There are a number of other published cases in which cytological examination of the pericardial fluid or pericardial biopsy was unhelpful (Hollingsworth and Sturgill, 1969; Hager *et al.*, 1970; Hansson *et al.*, 1970; Patt *et al.*, 1974; Poole-Wilson *et al.*, 1976). Nevertheless, open pericardial biopsy or thoracotomy remain the most fruitful methods of diagnosis.

In our second case a cardiac tumour was diagnosed shortly before death by angiocardiography. In this case the unusual features were the spontaneous resolution of the pericardial effusion and the appearance of an outpouching of the right atrium at the first angiocardiogram. In retrospect the latter feature was probably produced by the tumour, though it was not suggestive of this at the time. Spontaneous resolution of pericardial effusion in this condition has not been described previously, though Patt *et al.* in 1974 described a case of resolution occurring after a single pericardiocentesis.

In neither of our cases did M-mode echocardiography show any evidence of a tumour. Echocardiography is an invaluable aid in the diagosis of pericardial effusion, but the M-mode technique may not be useful in detecting pericardial or myocardial tumours. Two-dimensional echocardiography is more likely to provide diagnostic information, as described by Ports *et al.* (1977).

We conclude nevertheless that the best methods of making the diagnosis of primary angiosarcoma of the heart are by open exploration of the heart and pericardium, and by angiocardiography. The former should enable a histological diagnosis to be made, though, as our first case illustrates, this is not invariably so. Angiocardiography should disclose a characteristic appearance of a tumour, though correct interpretation may be difficult, as our second case illustrates.

The second case was under the care of Dr Malcolm Towers and Dr A. J. Moon, and we are grateful to them for permision to publish this case, to Dr B. E. Heard and Dr A. J. Salsbury of Brompton Hospital for the report of the histological findings in the pericardial biopsy in the first case, and to Dr A. Pomerance of Harefield Hospital for the necropsy and figures of the second case.

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Sinus node dysfunction associated with absence of right superior vena cava

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From St. Bartholomew's Hospital, London

SUMMARY A 41-year-old man presented with dizziness associated with sinus bradycardia and sinus arrest. An attempt to implant a transvenous pacing lead was frustrated by absence of the right superior vena cava. The left superior vena cava persisted and drained via the coronary sinus into the right atrium. Absence of the right superior vena cava may present with symptomatic sinus node dysfunction and may require an epicardial demand pacing system.

There are many causes of sinoatrial dysfunction, but disturbances of the blood supply to the sinus node (Lippestad and Marton, 1967) and local atrial pathology (Ferrer, 1968) constitute the majority. With the exception of atrial abnormalities, congenital cardiac anomalies are rarely associated with the sick sinus syndrome. The normal sinus node is situated at the junction of the right superior vena cava with the right atrium, but when the superior vena cava fails to connect directly with the right atrium the integrity of the sinus node may be jeopardised. We report such an instance when severe symptomatic sinus bradycardia and sinus arrest was encountered in a patient with an absent right superior vena cava.

Case report

A 41-year-old man was admitted for the investigation of recent presyncopal attacks. His past history included numerous syncopal episodes as a child and young man. His wife volunteered that his pulse rate had been slow for many years and an electrocardiogram recorded in 1960 had shown sinus bradycardia. On admission, he had an irregular pulse at 48 beats per minute and a blood pressure of 105/60 mmHg. There was a grade 2/6 mid-systolic ejection murmur at the left sternal edge. The remainder of the physical examination was normal.

The admission electrocardiogram showed a slow sinus rate with multiform atrial, junctional, and ventricular escape beats. The ventricular morphology of the conducted beats was normal. A 24-hour taped electrocardiogram confirmed the presence of profound sinus bradycardia with rates as low as 35 beats per minute and short episodes of sinus arrest (Fig. 1A). Symptoms of dizziness and lightheadedness were associated with both the bradycardia and brief spells of atrial fibrillation with a mean ventricular response of 140 beats per minute. An intracardiac electrophysiological study showed normal conduction intervals during the dominant rhythm when atrial activation arose in the region of the high right atrium (Fig. 1B). No other consistent site of sustained impulse origin was established though there were numerous atrial and junctional escape beats. After atrial pacing at 130 beats per minute for 1 minute, sinus node suppression exceeded 5 seconds. At other times, the immediate post-pacing pause was significantly shorter than the second post-pacing sinus interval (Fig. 1C).

The chest *x*-ray film showed a normal-sized heart and no pulmonary pathology. In retrospect the right superior vena caval shadow was absent (Fig. 2). A right subclavian venogram confirmed the absence of the right superior vena cava. Contrast crossed the midline and entered a persistent left-sided superior vena cava, which drained into the right atrium via the coronary sinus.

The history of presyncopal spells associated with bradycardia necessitated the implantation of a permanent pacemaker. An attempt was made to pass a permanent pacing lead via the persistent left superior vena cava, coronary sinus, and right atrium (Fig. 3) into the right ventricle. It was not possible to achieve a stable right ventricular apical pacing

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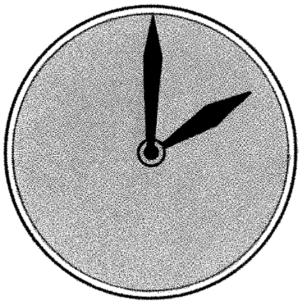

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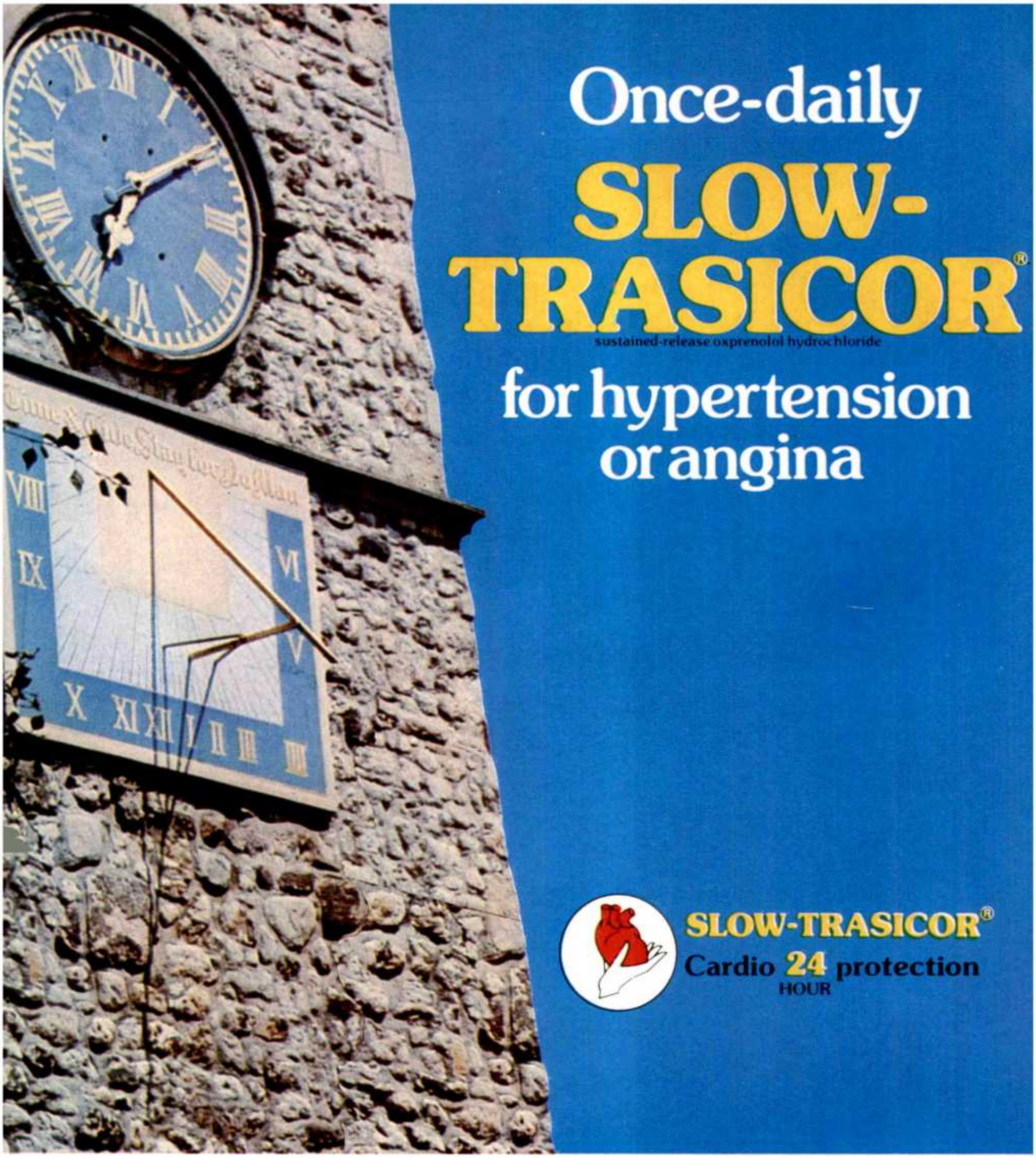
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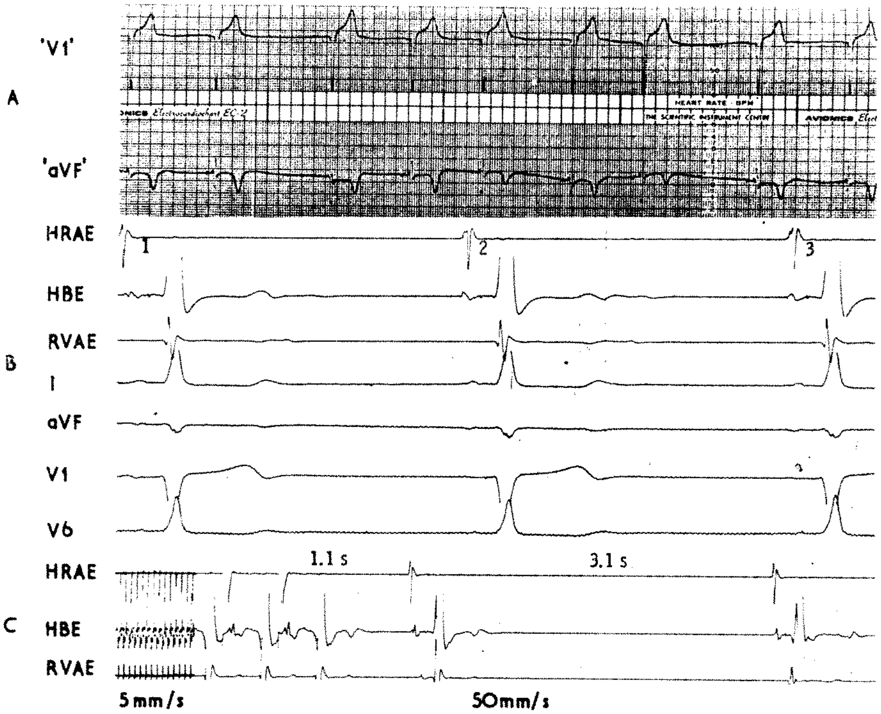

Fig. 1 *(A) Part of a 24-hour electrocardiogram, showing sinus bradycardia (PP 1·9 s), sinus arrest, and junctional escape. (B) A section of recording made during electrophysiological study. HRAE, high right atrial electrogram; HBE, His bundle electrogram; RVAE, right ventricular apical electrogram; I, aVF, V1, and V6, simultaneous surface electrocardiograms. Complex 1 arises in the high right atrial region, whereas complexes 2 and 3 arise from other atrial foci. (C) Rapid atrial pacing at 130 beats/minute (cycle length 460 ms) results in severe sinus node suppression. The immediate post-pacing pause is 1100 ms and the second pause 3100 ms.*

site and it was, therefore, necessary to implant an epicardial system. A permanent pacing electrode was sewn on to the lateral left ventricle through a limited left anterior thoracotomy.

Bouts of atrial fibrillation continued postoperatively, but were controlled with oral disopyramide 100 mg q.d.s. The patient was discharged and has since been free of symptoms.

Discussion

During the eighth week of intrauterine life the brachiocephalic vein develops as a bridge between the left and right cardinal veins and channels most of the blood from the left cardinal vein to the right. The left superior cardinal vein below the brachiocephalic anastomosis diminishes in size and forms the left superior intercostal vein, the oblique vein of the left atrium, and the coronary sinus (Marshall, 1850). The superior vena cava develops from the right superior cardinal vein. Persistence of the left anterior cardinal vein in the form of a left-sided superior vena cava occurs in 0·5 per cent of the population (Steinberg *et al.*, 1953). In patients with other congenital cardiac anomalies the incidence of a persistent left superior vena cava is increased to between 3 and 10 per cent (Campbell and Deuchar, 1954; Sipilä *et al.*, 1955; Fraser *et al.*, 1961). Absence of a patent right superior vena cava occurs in only 10 per cent of patients with a persistent left superior vena cava (Winter, 1954). In this situation, the right superior vena cava is usually completely absent, but in a small proportion an atretic cord remains (Karnegis *et al.*, 1964).

Absence of a patent right superior vena cava in the patient reported here was suggested by the plain chest *x*-ray film and confirmed angiographically by injection of contrast into the right subclavian vein. Since no other structural cardiac abnormality was present in this patient, the isolated persistence of

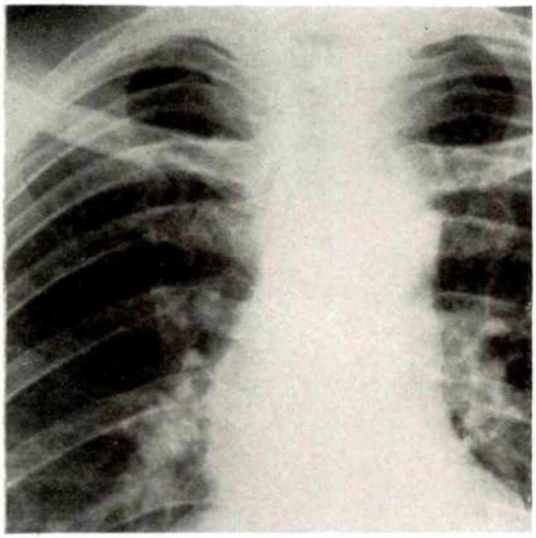

Fig. 2 *Part of the plain chest* x-*ray film which illustrates the absence of the right-sided superior vena cava.*

the left superior vena cava with absence of the right superior vena cava represents a rare variation of this anomaly.

The specialised pacemaker cells which eventually evolve to form the sinus node originate in the sinus venosus (Brooks and Lu, 1972). When the sinus venosus is absorbed into the right atrium these specialised cells come to lie around the base of the superior vena cava. Abnormal development of the right horn of the sinus venosus and right superior cardinal vein may jeopardise the normal development of the sinoatrial node and result in abnormal sinus node function.

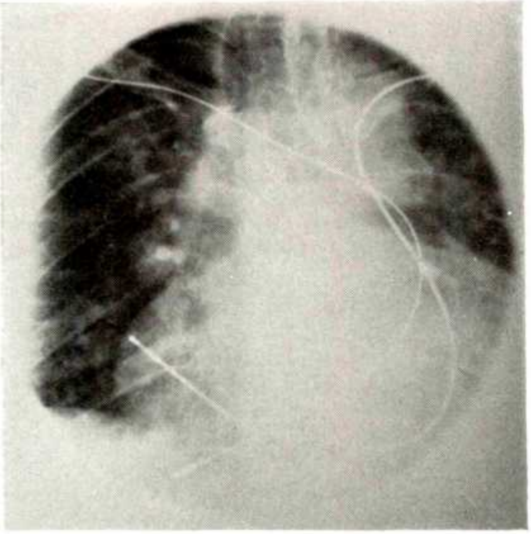

Fig. 3 *Anteroposterior chest* x-*ray film showing the course of both a temporary and permanent pacing lead through the persistent left-sided superior vena cava and coronary sinus into the right atrium.*

Our patient presented with a long history of sinus bradycardia and the recent onset of symptoms related to both bradycardia and short paroxysms of atrial fibrillation. The diagnosis of sick sinus syndrome with frequent, though unreliable, atrial, junctional, and ventricular escape beats was made from 24-hour electrocardiographic tape monitoring. The surface electrocardiographic P wave vector of the dominant rhythm was normal and intracavitary catheter mapping confirmed that the impulses arose from the high right atrium. Though the location of the primary pacemaker was electrophysiologically normal its generator reliability, as assessed by overdrive suppression, was abnormal. The maximum sinus node recovery time exceeded 5 seconds (Mandel *et al.*, 1971). No attempt was made to derive corrected values for the recovery time because of the large variability of pre-pacing sinus intervals. The second post-pacing pause was frequently considerably longer than the immediate post-pacing escape interval. This response is common in cases of sinus node dysfunction (Benditt *et al.*, 1976) and is thought to result from sinus node entrance block.

Sinus node dysfunction has been briefly reported in a case of persistent left superior vena cava (Winter, 1954), and 'nodal rhythms' (Nadas and Fyler, 1972) and ectopic atrial rhythms (Mantini *et al.*, 1966) have been observed in other cases. No histological evidence for ectopic sinoatrial nodal tissue was found in the patient reported by Mantini. Absence of the right superior vena cava may not significantly displace the anatomical location of the primary pacemaker but in this case was associated with severe sinoatrial node dysfunction.

The diagnosis of symptomatic bradycardia required the implantation of a permanent pacemaker. The tortuous course of the permanent pacing lead through the left-sided superior vena cava, coronary sinus, and right atrium resulted in unstable endocardial ventricular pacing. An epicardial pacing system is required when a persistent left superior vena cava is associated with absence of a patent right superior vena cava.

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A case of isolated primary chylopericardium

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SUMMARY Primary chylopericardium presented as radiographic cardiomegaly in an asymptomatic 19-year-old man. Normal findings at cardiac catheterisation and angiographic demonstration of cardiac displacement from the diaphragm suggested a collection of fluid below the heart which was confirmed by M and B mode ultrasound scanning. Thoracic blood pool isotope scanning indicated that the lumen was a pericardial effusion rather than a cyst. Lymphangiography did not indicate any direct lymphatic communication though a small pool of contrast appeared in the pericardium and the diagnosis of chylopericardium was confirmed by pericardiocentesis.

Surgical treatment was undertaken after rapid reaccumulation of chyle and the patient remains well 6 months later.

Case report

An asymptomatic 19-year-old male army recruit was referred for investigation of an enlarged heart shadow noted on routine chest radiography. There was no relevant medical history apart from an accident at the age of 10 when a fall from a trampoline caused painful hyperextension of the back; this was not treated medically. Physical examination was normal. In particular, on palpation of the cardiac apex, the jugular venous pressure and auscultation were normal. The arterial blood pressure was 120/70 mmHg without paradox.

A chest radiograph showed cardiomegaly (cardiothoracic ratio 0·53), with pyriform outline and the lung fields were clear. The lateral radiograph showed a diminished anteroposterior diameter and a 'straight back'. A curved shadow lying within the mediastinal border was thought to represent the apex of the left ventricle and was visible in both posteroanterior and lateral films (Fig. 1). Electrocardiography was normal, with a mean frontal plane QRS axis of +90°. M mode echocardiography, with the transducer conventionally placed at the fourth left intercostal space just lateral to the sternum, failed to show any abnormality in spite of caudal direction of the ultrasound beam. Cardiac catheterisation was, therefore, undertaken and showed normal right and left-sided pressures. The right and left ventriculograms were normal, but the heart was separated from the left hemidiaphragm by an unopacified area of similar radiographic density to the cardiac shadow. In view of this appearance M mode echocardiography was repeated with the transducer positioned in the sixth left intercostal space near the midclavicular line. There was an echo-free space inferior to the left ventricular myocardium, which was compatible with a pericardial effusion or cyst (Fig. 2).

Contact grey scale B scan ultrasound[1] images with the patient supine were recorded from several positions on the lower anterior chest wall and left upper abdominal quadrant. These showed a thin-walled echo-free space bounded superiorly by the heart and inferiorly by the left hemidiaphragm. It extended anteriorly to the chest wall and posteriorly to the lung (Fig. 3). The technique later proved to be a valuable aid to pericardiocentesis. A thoracic blood pool isotope scan after intravenous injection of 3 mCi Technetium 99m-labelled albumin showed abnormal imaging of the heart, with a 'halo' surrounding the cardiac silhouette typical of pericardial effusion (Staab and Patton, 1973) (Fig. 4).

Lymphangiography with injection of 7 ml 'Lipiodol' into each foot showed normal abdominal lymphatics. The thoracic duct was not visualised. A small pool of contrast which collected later in the pericardium was seen in the erect position and moved with gravity. The site of communication between lymphatic channels and the pericardial sac was not demonstrated.

Percutaneous pericardiocentesis yielded 750 ml fluid which had the appearance and chemical

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[1] Nuclear Enterprises Diasonograph NE 4102 with NE 4804 Grey-Scale attachment.

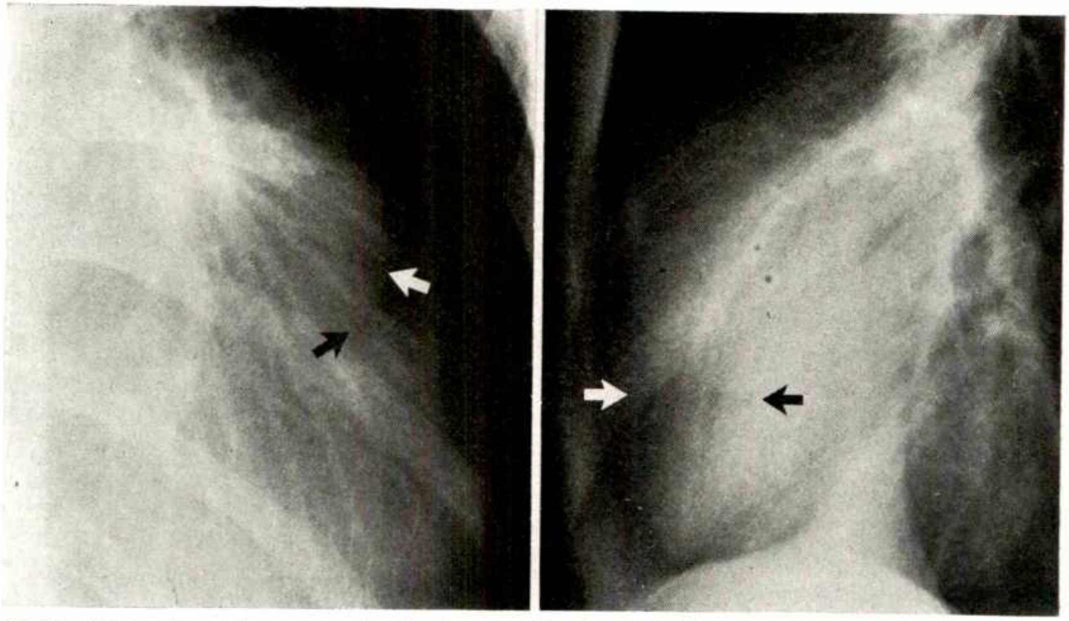

Fig. 1 *Chest radiograph at presentation showing curved border of the left ventricle within the pericardial effusion.*

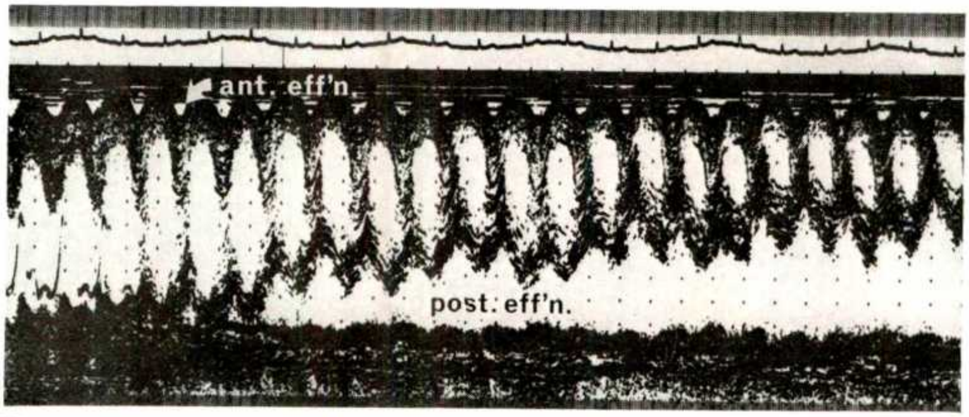

Fig. 2 *M mode echocardiographic scan recorded with the transducer in the sixth left intercostal space and showing a small anterior echo-free space and a large posterior echo-free space.*

characteristics of chyle (Table). Chest radiography one hour after aspiration showed a cardiothoracic ratio of 0·40. There was a small amount of air in the upper pericardial sac. The electrocardiogram remained unchanged. Chest radiograph repeated after 72 hours showed reaccumulation of fluid. The patient remained asymptomatic with normal physical findings.

At thoracotomy an excess of 500 ml chyle was drained from the pericardial space. The heart and pericardium were otherwise normal; the thoracic duct could not be identified in the mediastinum but two small structures thought to be lymphatic channels were sutured. No other communication was seen between the lymphatics and pericardial cavity. Subtotal pericardiectomy with abrasion of remaining posterior surfaces was performed.

The postoperative course was uneventful. Two months later he was asymptomatic with normal physical signs. Chest *x*-ray film showed a normal

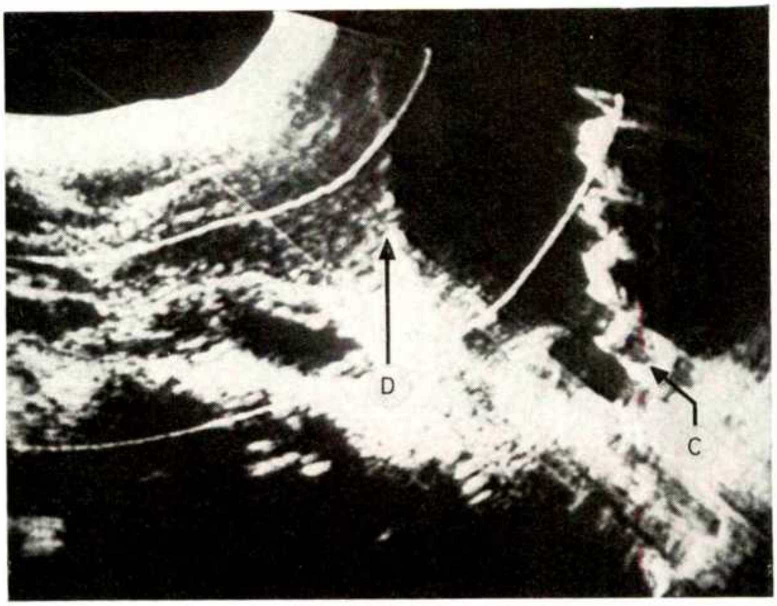

Fig. 3 *Contact grey scale B-scan ultrasound image showing abnormal separation of diaphragm (D) from the moving lower cardiac border (C) by an echo-free space. The image is approximately sagittal, with the patient supine (head to the right).*

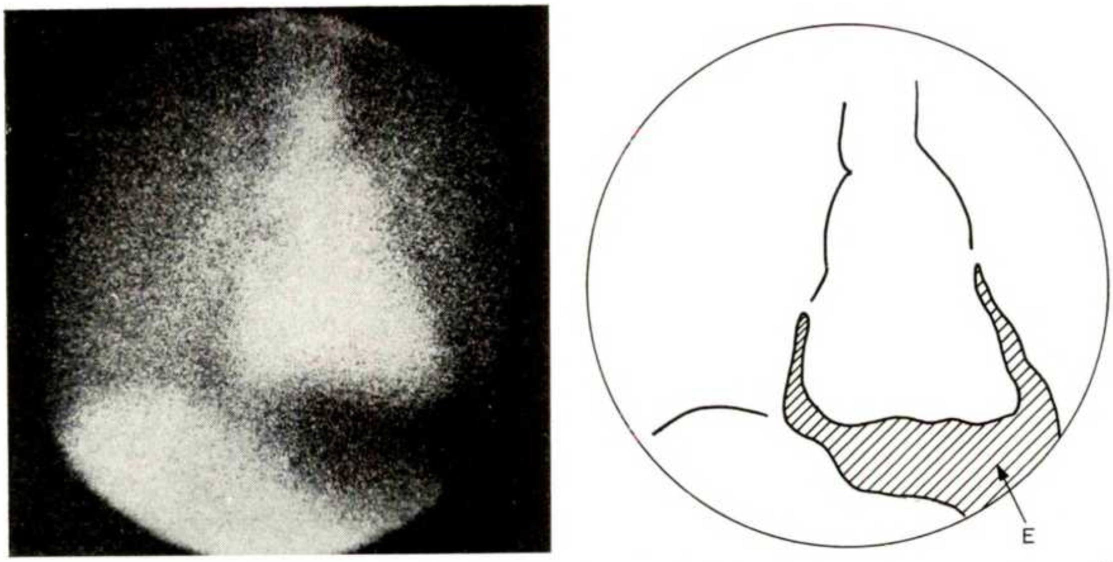

Fig. 4 *Thoracic blood pool scan showing abnormal 'halo' surrounding the cardiac silhouette. It is a U-shaped area of decreased radioactivity caused by absorption of the background radiation by the pericardial fluid. Note the area separating the left hemidiaphragm from the base of the heart representing the inferior localisation of the chylous effusion (E).*

cardiac silhouette (cardiothoracic ratio 0·40) with no evidence of reaccumulation of fluid. The electrocardiogram showed slight ST segment and T wave changes consistent with pericardiectomy and a change of mean frontal QRS axis to +60°. A repeat of the B mode and M mode echocardiograms and thoracic isotope blood pool scan confirmed the absence of pericardial fluid.

Table *Composition of fluid obtained at pericardiocentesis*

Appearance	Milky yellow	
Osmolarity	288 mmol/l	
Cholesterol	2·4 mmol/l	(92·3 mg/100 ml)
Triglycerides	15·0 mmol/l	(1363·6 mg/100 ml)
Protein	96 g/l	
Glucose	4·9 mmol/l	(87·5 mg/100 ml)
Sodium	140 mmol/l	
Potassium	3·9 mmol/l	
Microscopy	Very cellular deposit composed almost entirely of mature lymphocytes	

Discussion

Isolated primary chylopericardium is a rare condition and aetiology remains obscure in most cases. The significance of the previous back injury in our patient is unknown. Only Naef (1956) previously mentioned external injury as a possible cause.

An asymptomatic presentation is not unusual. Of the 22 patients reviewed by Dunn (1975), 8 were asymptomatic when first seen though only 2 were thought to be entirely normal on physical examination.

Diagnosis is by recognition of the presence of a pericardial effusion and demonstration of its chylous nature by pericardiocentesis. In our case the initial diagnosis presented some difficulties and a number of noninvasive techniques were used to overcome them.

Contact grey scale B-scan ultrasound scanning was useful in defining the fluid and localising the site for aspiration. It suggested a cystic cavity lying almost entirely below the heart, even with the patient supine. This inferior localisation of the chyle was possibly related to the chronicity of the effusion and to the narrow anteroposterior chest diameter. M mode echocardiography was initially unhelpful when performed from the usual transducer position in the fourth left intercostal space but it was subsequently successful in showing pericardial fluid when performed from a more inferior position. More inferior transducer positions should, therefore, be routine when standard echocardiographic techniques fail to show a suspected pericardial effusion. Further evidence for the pericardial site of the fluid was obtained by thoracic isotope blood pool scanning after injection of 99m-Technetium labelled albumin which showed the 'halo' sign typical of pericardial effusion. These techniques proved particularly useful in confirming the absence of fluid after operation.

An interesting and possibly unique radiographic feature was the visualisation of the cardiac border within the outline of the pericardial sac on plain chest radiography. This could be the result of the high fat content and relative transradiancy of chyle compared with heart and blood. It may be a useful early diagnostic clue to the chylous nature of the pericardial fluid.

Surgery was undertaken because the chylous effusion reaccumulated rapidly after pericardiocentesis and it was felt that associated operable tumours such as lymphangiomas and hygromas could not otherwise be definitely excluded.

It is most important that, if it can be identified, the thoracic duct be ligated at operation as all 17 previously reported cases eventually treated with thoracic duct ligation and partial pericardiectomy have survived, with no reaccumulation of fluid. Of 6 previously reported patients who have been treated with partial pericardiectomy alone, 3 required reoperation (with thoracic duct ligation) because of reaccumulation of fluid, 2 died before operation, and 1 refused reoperation. In our case the thoracic duct could not be identified with certainty, but 2 small lymphatic channels were suture ligated and partial pericardiectomy was carried out with abrasion of the remaining surfaces in order to seal off any remaining sites of lymphatic communication. Therefore, if the thoracic duct cannot be identified it seems advisable to seal all lymphatic channels which can be found.

Previous case reports indicated that absence of reaccumulation of chyle after operation was associated with an excellent long term prognosis and this is, therefore, expected in our case.

We thank Dr R. W. Emanuel for advice in the preparation of this report on his patient and Mr M. F. Sturridge (Department of Cardiothoracic Surgery, The Middlesex Hospital) for advice on surgical management and preparation of this report.

We acknowledge the assistance of Dr P. J. Ell (Department of Nuclear Medicine, The Middlesex Hospital) and Dr W. Lees (Department of Clinical Measurement, The Middlesex Hospital).

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Notices

British Heart Journal, 1979, **41**, 512

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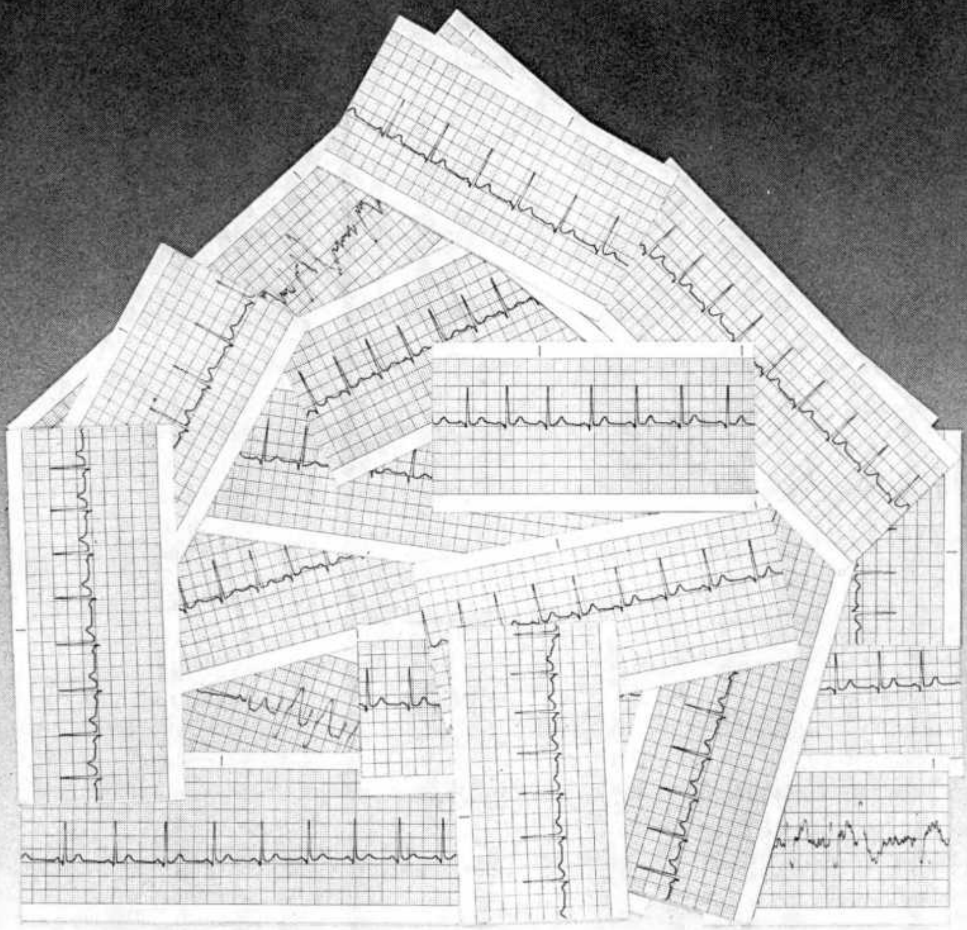

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Rotational excursion of heart in massive pericardial effusion studied by phased-array echocardiography *H. Matsuo, M. Matsumoto, Y. Hamanaka, T. Ohara, S. Senda, M. Inoue, and H. Abe* 513

Evaluation of posterior aortic wall echogram in diagnosis of mitral valve disease *R. J. C. Hall, S. E. Clarke, and D. Brown* 522

Determination of pressure gradient in mitral stenosis with Doppler echocardiography *Jarle Holen and Svein Simonsen* 529

Echocardiography in cardiovascular drug assessment *M. A. Martin and N. R. J. Fieller* 536

Nomenclature and classification of congenital heart disease *M. J. Tynan, A. E. Becker, F. J. Macartney, M. Quero Jiménez, E. A. Shinebourne, and R. H. Anderson* 544

Prevalence of congenital heart disease in black schoolchildren in Soweto, Johannesburg *M. J. McLaren, A. S. Lachman, and J. B. Barlow* 554

How to determine atrial situs? Considerations initiated by 3 cases of absent spleen with a discordant anatomy between bronchi and atria *G. Caruso and A. E. Becker* 559

Evaluation of thallium-201 exercise scintigraphy in coronary heart disease *R. G. Murray, J. H. McKillop, R. G. Bessent, J. G. Turner, A. R. Lorimer, I. Hutton, W. R. Greig, and T. D. V. Lawrie* 568

Thallium-201 scintigraphy in diagnosis of coronary stenosis. Comparison with electrocardiography and coronary arteriography *R. A. Corne, M. S. Gotsman, A. Weiss, D. Enlander, L. D. Samuels, Jean A. Salomon, B. Warshaw, and H. Atlan* 575

Effects of oxygen administration, bicarbonate infusions, and brief hyperventilation on patients with pulmonary vascular obstructive disease *Geoffrey Morrison and Fergus Macartney* 584

Haemodynamic studies in veno-occlusive disease of the liver *T. E. Kasturi, S. C. Manchanda, R. K. Tandon, M. Rajani, and M. L. Bhatia* 594

Electrophysiological and haemodynamic basis for application of new pacemaker technology in sick sinus syndrome and atrioventricular block *Richard Sutton and Paul Citron* 600

Cardiomyopathic syndrome caused by coronary artery disease. III: Prospective clinicopathological study of its prevalence among patients with clinically unexplained chronic heart failure *C. A. Boucher, J. T. Fallon, R. A. Johnson, and P. M. Yurchak* 613

Case reports

- Marfanoid hypermobility syndrome associated with coarctation of the aorta *A. Daneshwar, D. Tavakoli, and J. Nazarian* 621
- Hypertrophic cardiomyopathy associated with sudden death during marathon racing *T. D. Noakes, A. G. Rose, and L. H. Opie* 624
- Polymyositis and complete heart block *John M. Reid and Ronald Murdoch* 628

Correspondence 630

Notices 632

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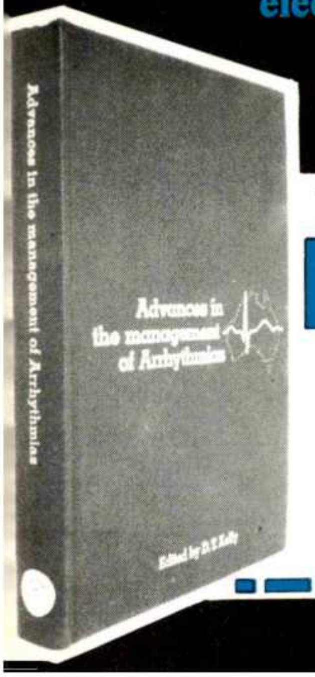
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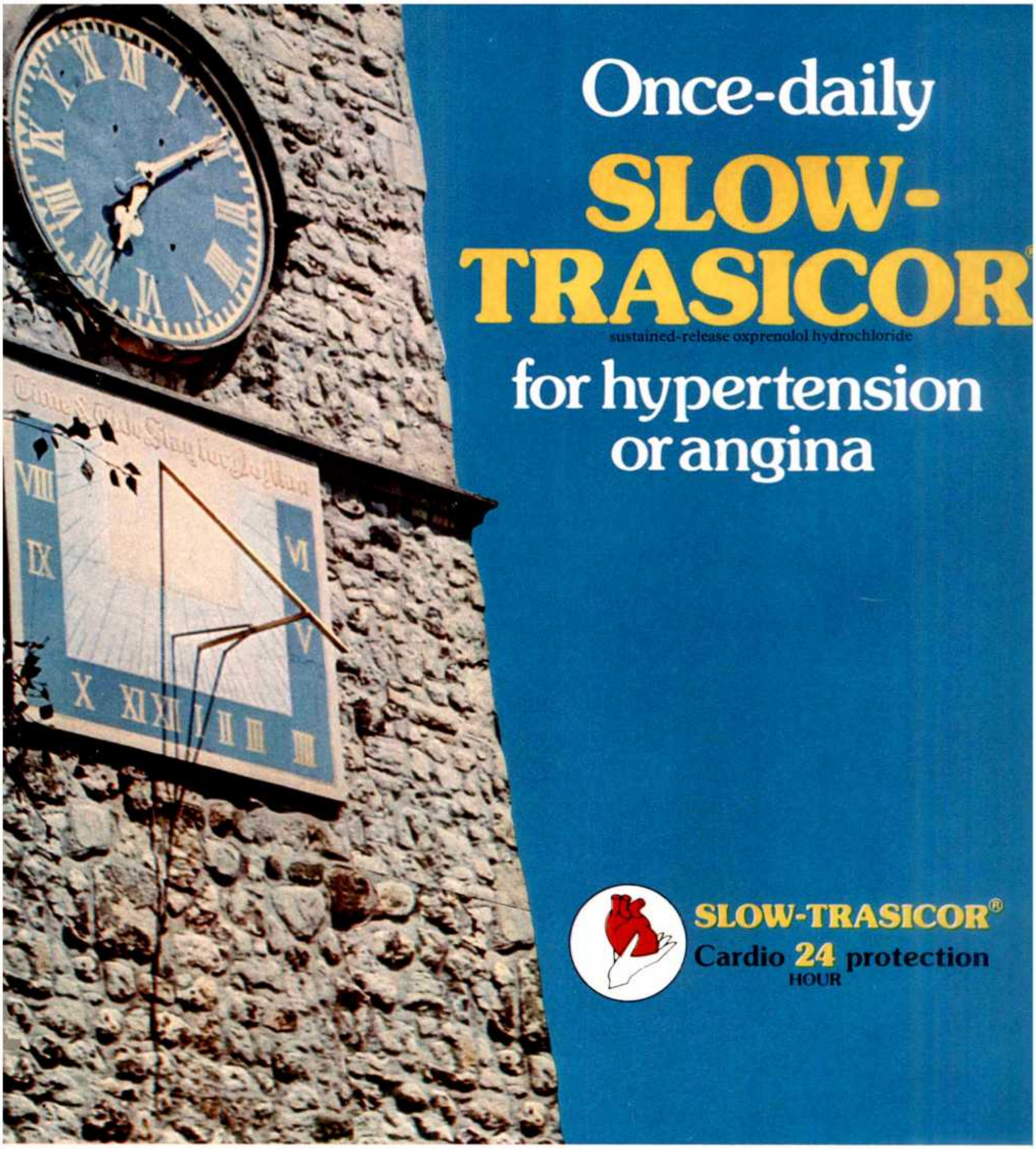
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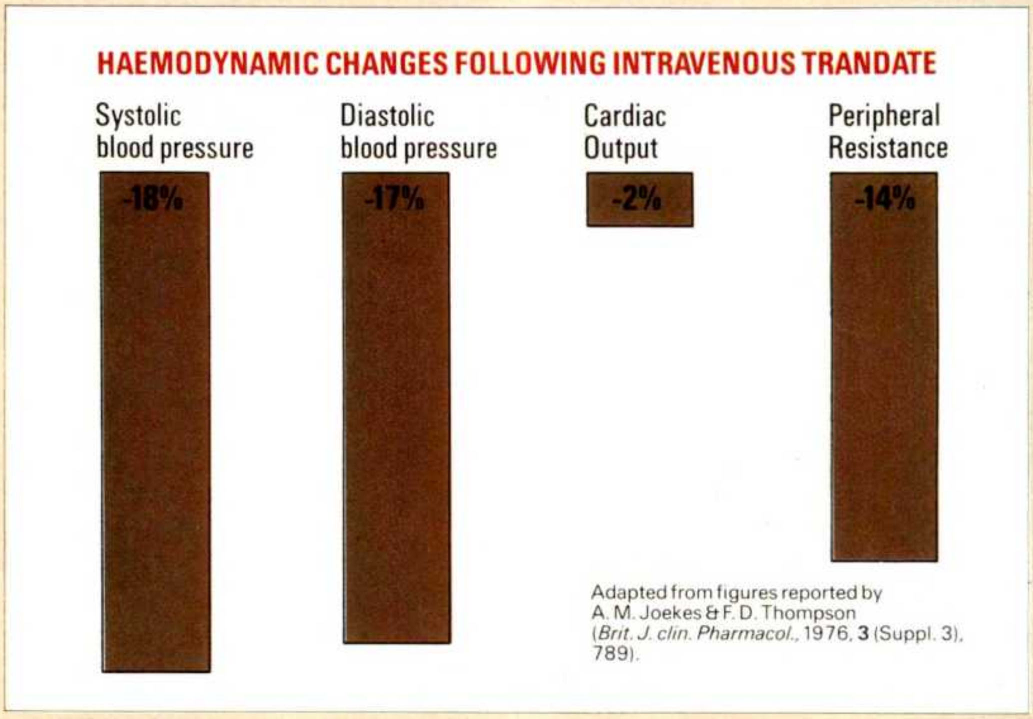

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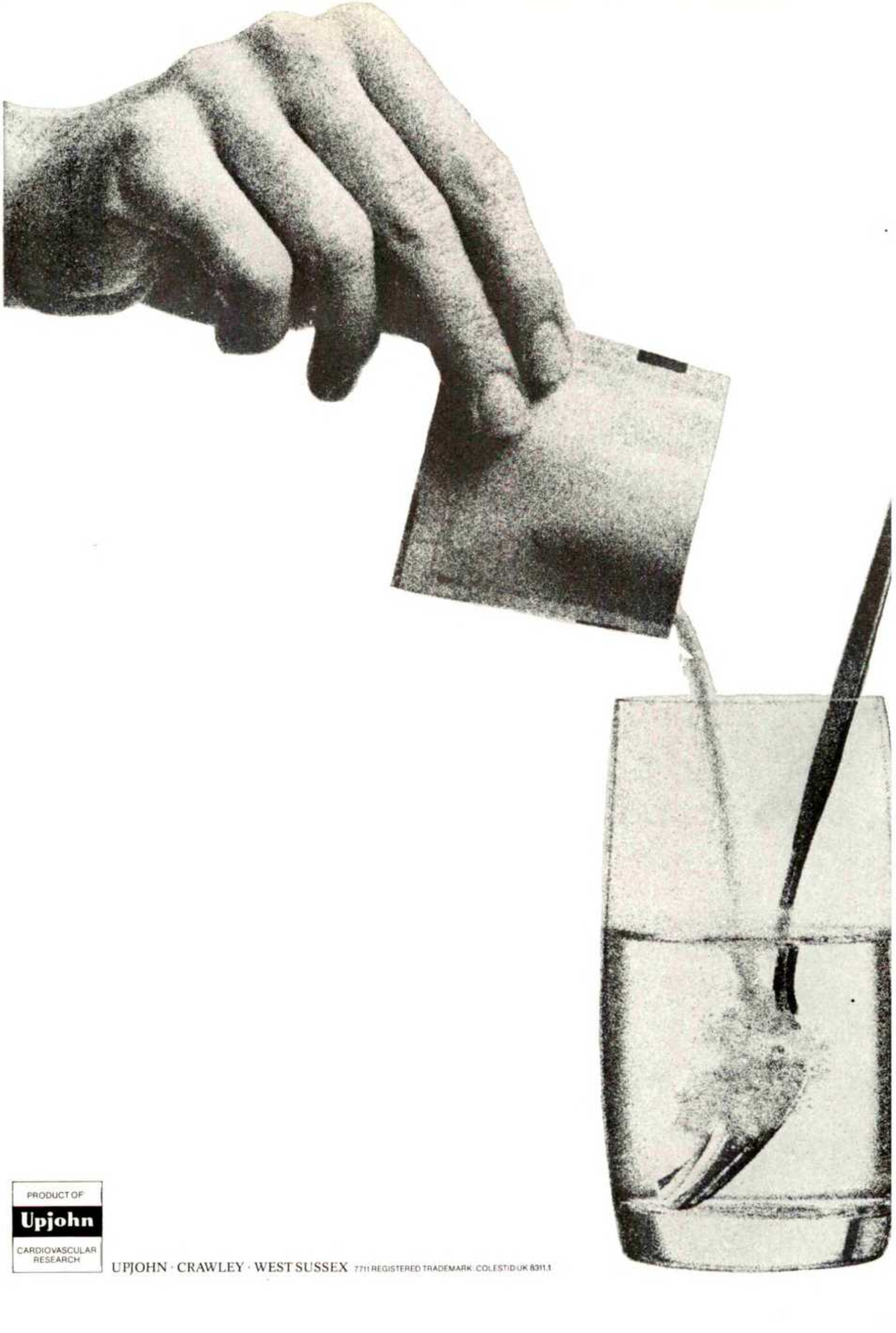

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References: 1. Med. J. Aust. (1973). *1*:1223.
2. JAMA (1972). 222:676.
3. New Zealand J. Med. (1972). 76:12.

Prescribing Information

Presentations: Tasteless and odourless granules of colestipol hydrochloride. *Uses:* Adjunctive therapy to diet for treatment of hypercholesterolaemia, particularly Frederickson Type II. *Dosage and Administration:* Always mix with water or other fluids before ingesting. Oral total daily dosage for adult 15–30 grams. Take in divided doses 2–4 times daily. *Contraindications:* Hypersensitivity to colestipol. *Precautions, Warnings:* Not to be taken in dry form. Colestid may interfere with absorption of some drugs (e.g. penicillin G, tetracycline, chlorothiazide). Safety for use in pregnant women or children not established. *Package Quantities:* 30 x 5 g sachets; 250 g bottle. Each sachet or scoopful contains 5 g colestipol hydrochloride. *Further Information:* Colestid is not absorbed. It binds bile acids causing further cholesterol conversion to bile acids thus lowering serum cholesterol levels. *Basic NHS Costs:* 30 x 5 g sachets £8.90. 250 g bottle £13.76. Product Licence Nos. PL 0032/0055. PL 0032/0057. *Full Product information is available on request.*

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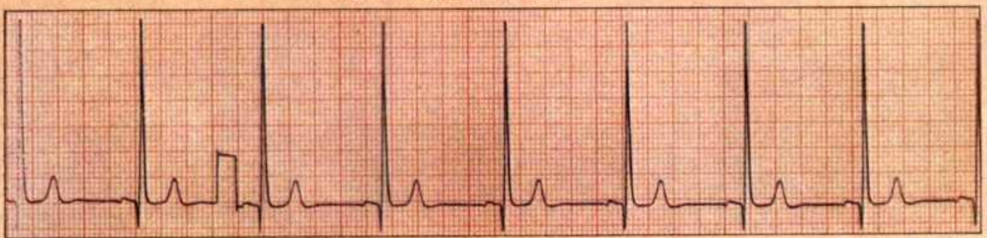

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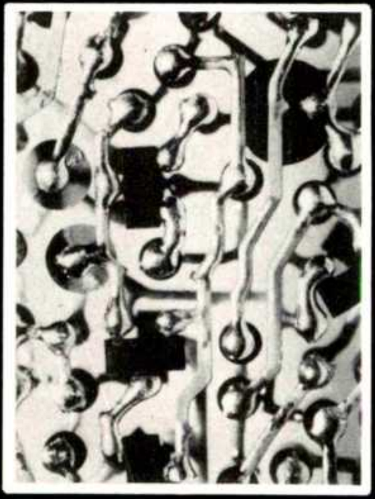

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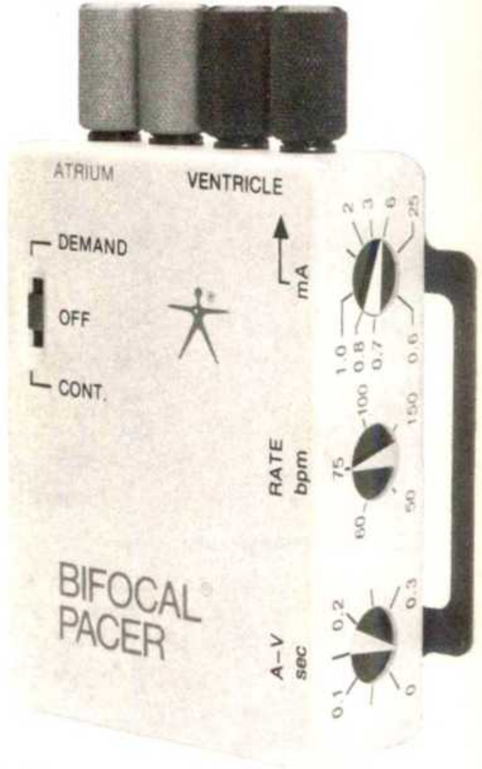

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British Heart Journal, 1979, **41**, 513-521

Rotational excursion of heart in massive pericardial effusion studied by phased-array echocardiography

HIROHIDE MATSUO, MASAYUKI MATSUMOTO, YASUHIKO HAMANAKA, TATSUHIKO OHARA, SHOHICHI SENDA, MICHITOSHI INOUE, AND HIROSHI ABE

From the First Department of Medicine, Osaka University Medical School, Fukushima-ku, Osaka, Japan

SUMMARY We have observed rotational excursion, comprising anteroposterior and right to left movement of the heart, and cardiac twist around the long axis in 2 patients with massive pericardial effusion, using a phased-array echocardiograph recently developed in this country.

Sagittal real-time cross-sections showed only the anteroposterior swing motion, but horizontal cross-sections revealed a counterclockwise rotational excursion and cardiac twist during this rotational excursion. The rotational excursion consisted of a rapid and almost straight movement right and posteriorly in systole, and a slow arcing excursion left and anteriorly in diastole. The speed of this movement was not uniform. The heart disclosed dominant counterclockwise twisting motions in mid to late systole and in late diastole, synchronous with atrial contraction. These movements were described relative to an external system of co-ordinates. Controls, consisting of a normal healthy subject, and cases with mitral stenosis, mitral regurgitation, and hypertrophic cardiomyopathy, did not show any rotational excursion. In the latter 2 diseases, cardiac twists were observed, but they were less dominant than in cases with massive pericardial effusion.

Since early days of this technique, echocardiography has been reported as a reliable, noninvasive diagnostic tool for massive pericardial fluid (Edler, 1955; Feigenbaum *et al.*, 1965, 1966). In a recent report on the simulated appearance of mitral valve prolapse and systolic anterior movement of the mitral valve in the presence of pericardial fluid, the existence of a rocking or rotary motion of the heart about its attachment to the great vessels in addition to an anteroposterior swing was suggested as a possible cause (Nanda *et al.*, 1976). Such a rotary motion in pericardial fluid, however, has not yet been demonstrated directly. In this study we have therefore investigated the motion of the heart in massive pericardial fluid in greater detail than has previously been undertaken, using phased-array echocardiography.

Subjects and methods

Two cases of benign idiopathic chronic pericarditis, diagnosed through clinical histories and examination, and 4 controls were chosen from our file and studied. Patients with massive pericardial effusion:

Case 1: A 72-year-old woman, whose cardiothoracic ratio was 87 per cent.
Case 2: A 65-year-old man, whose cardiothoracic ratio was 80 per cent.

Neither of these cases with pericardial effusion showed electrical alternans or cardiac tamponade.

Controls: These consisted of a normal healthy 28-year-old man (one of our colleagues); a 38-year-old woman with mitral stenosis; a 21-year-old woman with mitral regurgitation, and a 68-year-old man with hypertrophic obstructive cardiomyopathy.

The prototype of a new commercially available electronic beam scanning echocardiograph (Hitachi EUB-10) was used and improved during this study. The frequency of ultrasound emitted was 2·3 MHz at a pulse repetition rate of 4608 Hz. The sector angle was 72° and the frame rate was 18 per second. The hand-held transducer, consisting of 32 small elements, had a diameter of 27 mm. The timing of Polaroid photographs of the real-time cross-sectional image of the heart during the cardiac cycle was displayed as an interruption of the electrocardiogram displayed on the cathode ray tube. In real-time observation and cine film recording, the end of the electrocardiogram represents the time of the image. Simultaneous recording of a standard echocardio-

Received for publication 30 May 1978

gram in a direction within the real-time cross-sectional echocardiogram was available using a slave cathode ray tube. Cross-sectional echocardiograms were recorded on Polaroid film and 8 mm cine film at a frame rate of 18 per second. Frames from one representative cardiac cycle were superimposed for

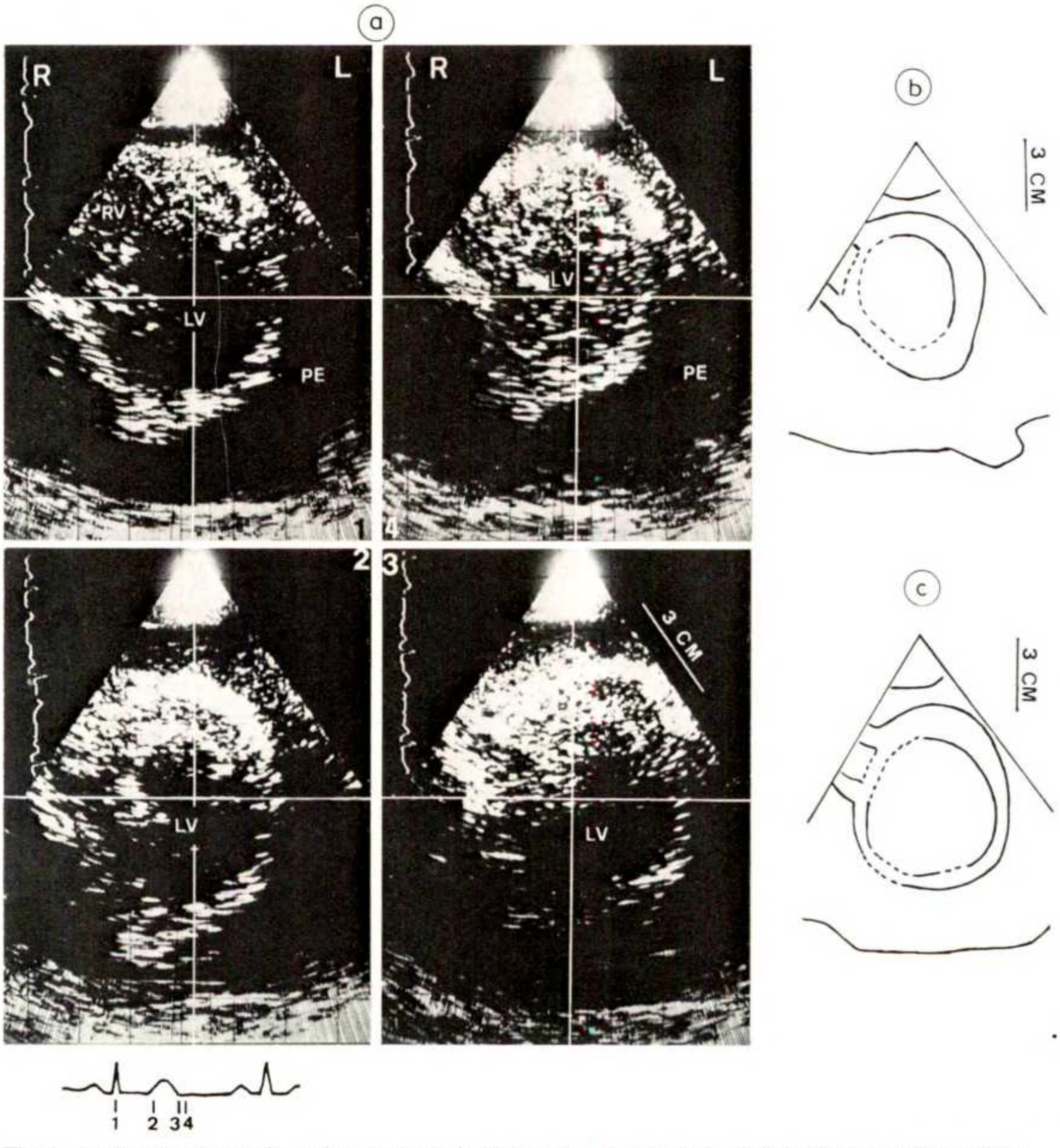


Fig. 1 *(a) Rotational excursion and cardiac twist in horizontal sections at the level of the chordae tendineae of the mitral valve. These horizontal cross-sections (panels 1 to 4) were obtained at the level of the chordae tendineae of the mitral valve. Panels numbered 1 to 4 were recorded on Polaroid films at 4 different times in the cardiac phase indicated with the schematic electrocardiogram at the bottom. The heart near the anterior chest wall (panel 1) moved posteriorly and slightly to the right (panel 2) in systole, and moved slowly to the left and anteriorly showing an arching motion in diastole (panel 3, 4). Schematic representations of panels 3 and 4 for deriving the heart contours are also shown (b) and (c). Abbreviations: R, right; L, left; PE, pericardial effusion; RV, right ventricle; LV, left ventricle.*

the analysis of cardiac motion using an external system of co-ordinates. In order to ensure consistency and minimise experimental error in tracing, we took as reference points the point of sound source and one crossing of division lines on the cathode ray tube at constant positions in each projection of the cine frame used for tracing.

Echocardiograms were recorded while patients held their breath at expiration in a supine position. The surface of the transducer was kept in contact with the skin surface by echo transmission jelly. Cross-sectional echocardiograms were recorded in horizontal sections and in sections along the short and long axes of the heart from the anterior chest wall.

Results

(1) REAL-TIME CROSS-SECTIONAL ECHOCARDIOGRAPHIC FINDINGS IN CASE 1

(*a*) *Horizontal cross-sections recorded at level of chordae tendineae of mitral valve*

Real-time observation of case 1 in horizontal section at the level of chordae tendineae for several minutes disclosed consistently a counterclockwise rotational excursion, made up of a combination of anteroposterior and right-to-left movement, and a twisting motion of the heart as it proceeded along its path. To show this excursion 4 representative cross-sectional echocardiograms recorded on Polaroid films at 4 different times in one cardiac phase are shown in Fig. 1. In this section the heart was near the anterior chest wall in early systole (Fig. 1, panel 1). As the contraction proceeded the heart showed a swift movement posteriorly and slightly to the right, taking its most posterior and medial position in mid-systole (Fig. 1, panel 2). In diastole the heart moved slowly to the left and anteriorly, showing an arcing motion (Fig. 1, panel 3), and came nearest to the anterior chest wall, nearing a position in early systole (Fig. 1, panel 4). Though the quality of the images in the Polaroid photographs as in Fig. 1 was not high, it was satisfactory for real-time observation. Rotational excursion of the heart and the magnitude of this excursion are shown in the superimposing of the contours of the whole heart (epicardium) at 4 different phases in 1 cardiac cycle (Fig. 2). These contours show a counterclockwise rotation in the course of 1 cardiac cycle.

(*b*) *Cross-sectional echocardiograms along short axis of heart at level near apex*

At a level near the apex of the heart the counterclockwise rotational excursion was more evident than at the level of chordae tendineae of the mitral valve in cross-sectional echocardiograms (Fig. 3). Superimposition of the contours of the whole of the heart in the 4 panels in Fig. 3 clearly shows this excursion motion of the heart (Fig. 4).

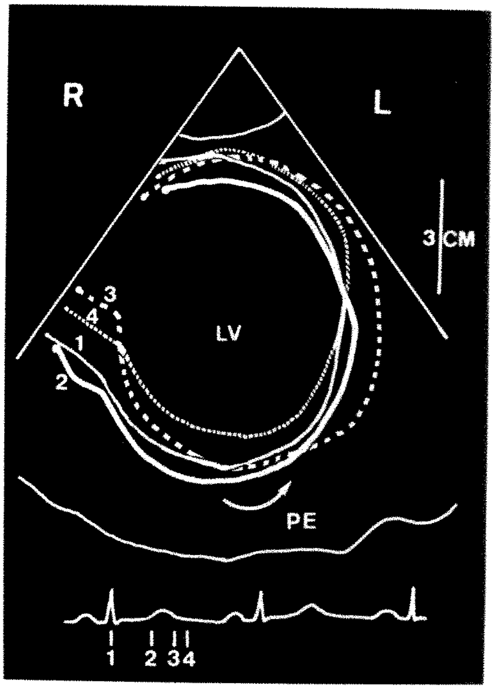


Fig. 2 *Superimposed contours of the whole of the heart of Fig. 1. These contours of the whole of the heart (epicardium) showed a counterclockwise rotational excursion in a cardiac cycle. The times in the cardiac phase of these contours are indicated with the schematic electrocardiogram at the bottom of this figure.*

(*c*) *Evidence of cardiac twist and rotational excursion in horizontal cross-section at level of interventricular septum*

Echoes from two points at the junction of the interventricular septum and left ventricular free wall (shown in the left panel of Fig. 5a), which were identifiable in all frames of a cardiac cycle, were successively superimposed to show the additional presence of cardiac twist superimposed on rotational excursion. Representative frames used in tracing are shown in Fig. 5b. Open circles for times 1 to 8 show the changes in position in systole and solid circles for times 9 to 19 show changes in position in diastole. The timing of these points in the diagram is shown with the schematic electrocardiogram. The tracing of both points showed significant counterclockwise rotational excursion during a cardiac cycle. The anterior point showed also counter-

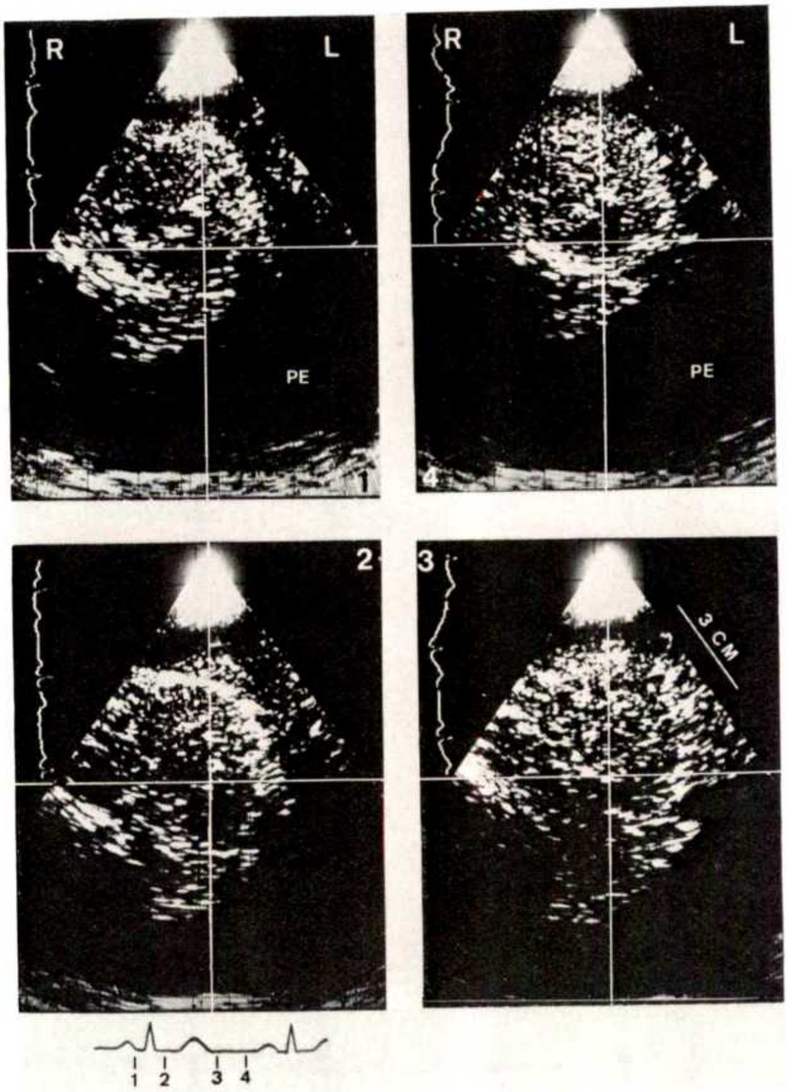


Fig. 3 *Rotational excursion and cardiac twist in a section along the short axis of the heart near the apex. These cross-sections were obtained near the apex of the heart. Panels 1 to 4 were recorded on Polaroid films at the times in the cardiac phase shown with the schematic electrocardiogram. In this plane the rotational excursion showed larger excursion than at the level of the chordae tendineae of the mitral valve.*

clockwise triangular motion, which corresponded to twisting motion, during times 5 to 8 in systole and during times 14 to 17, atrial systole. The posterior point, however, did not show twisting motion.

In order to show cardiac twist, the angle of the midline of the interventricular septum to the anterior chest wall was measured successively and shown with open and solid circles in polar coordinates of Fig. 5a (right lower panel).

In this analysis dominant deflections, which indicated twist motions, were observed in mid to late systole, during times 4 to 8, and in accordance with atrial systole during times 14 to 18. The anterior point and midline of the interventricular

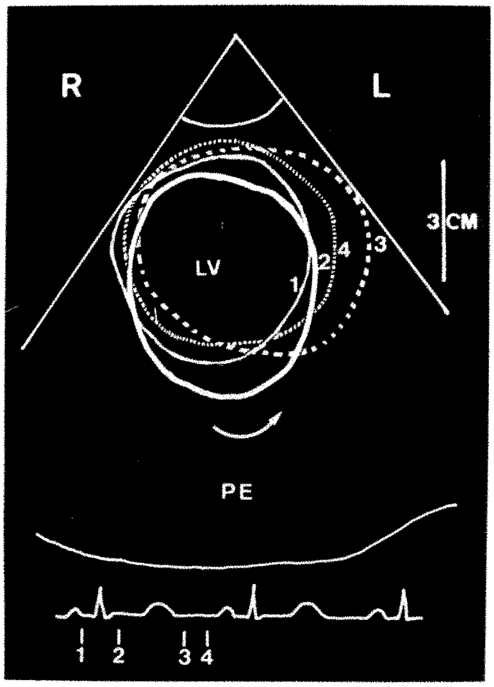


Fig. 4 *Superimposed contours of the whole of the heart of Fig. 3. A large counterclockwise rotational excursion was clearly shown in this figure. The times in the cardiac phase of these contours are indicated with the schematic electrocardiogram at the bottom of this figure. The leftward shift was largest in early diastole.*

septum showed similar twisting motions, but the posterior point did not show a twisting motion. The difference in motions among these may be attributed to that of their mobility resulting from anatomical differences.

(*d*) *Cross-sectional echocardiograms along long axis of heart and standard echocardiogram within the section*

Anteroposterior swing motion of the heart was observed in cross-sectional echocardiograms (Fig. 6 right and centre panels), as reported previously (Matsuo *et al.*, 1975). The heart was located posteriorly in mid-systole (centre panel), and anteriorly in diastole (right panel). The anteroposterior dimension of the left ventricle in mid-diastole was smaller than in end-systole in another echocardiographic cross-section along the long axis of the heart using stop action technique, suggesting the presence of lateral swing of the heart.

A standard M-mode echocardiogram was recorded with an ultrasound beam shown as a white line in the centre and right cross-sections penetrating the anterior right ventricular wall, interventricular septum anterior mitral leaflet, and left atrioventricular groove. This echocardiogram showed a systolic posterior bowing movement on the anterior mitral leaflet, mimicking mitral valve prolapse, and a characteristic sharp posterior motion (arrow) of the epicardial surface of the left atrioventricular groove synchronous with atrial contraction. The latter seemed to correspond to the cardiac twist resulting from atrial contraction observed in the horizontal and short axis cross-sectional echocardiograms.

(*e*) *Disappearance of rotational excursion in horizontal cross-section after diminution of pericardial fluid*

A year after the initial examination by the present method a spontaneous and pronounced diminution of pericardial fluid was noted. The cardiothoracic ratio was reduced from 87 to 65 per cent. The rotational excursion of the heart was no longer seen by real-time horizontal cross-sectional echocardiography at the level of the chordae tendineae of the mitral valve. Only the cardiac twist, less dominant than before, was observed.

(2) REAL-TIME CROSS-SECTIONAL ECHOCARDIOGRAPHIC FINDINGS IN CASE 2

The rotational excursion of the heart in horizontal cross-sectional echocardiograms of this case was smaller than in case 1 (Fig. 7). Total cross-sectional echocardiographic observations in this case, including the long axis cross-sections, suggested a localisation of pericardial fluid, a lack of smoothness of rotational excursion, and a partial adhesion of the epicardium to the pericardium.

(3) REAL-TIME CROSS-SECTIONAL ECHOCARDIOGRAPHIC OBSERVATION IN CONTROLS AT LEVEL OF CHORDAE TENDINEAE OF MITRAL VALVE

Four subjects (normal healthy, mitral stenosis, mitral regurgitation, hypertrophic obstructive cardiomyopathy) were chosen as controls from our file. None of these showed rotational excursion of the heart. The cardiac twist in late diastole was observed in cases with mitral regurgitation and hypertrophic obstructive cardiomyopathy, but this was less dominant than in massive pericardial effusion.

Discussion

The initial echocardiographic report on massive pericardial effusion was made by Edler in 1955. In the same year the possibility of rotatory oscillation of the heart associated with electrical alternans in massive pericardial effusion was suggested by McGregor and Baskind (1955). Feigenbaum and

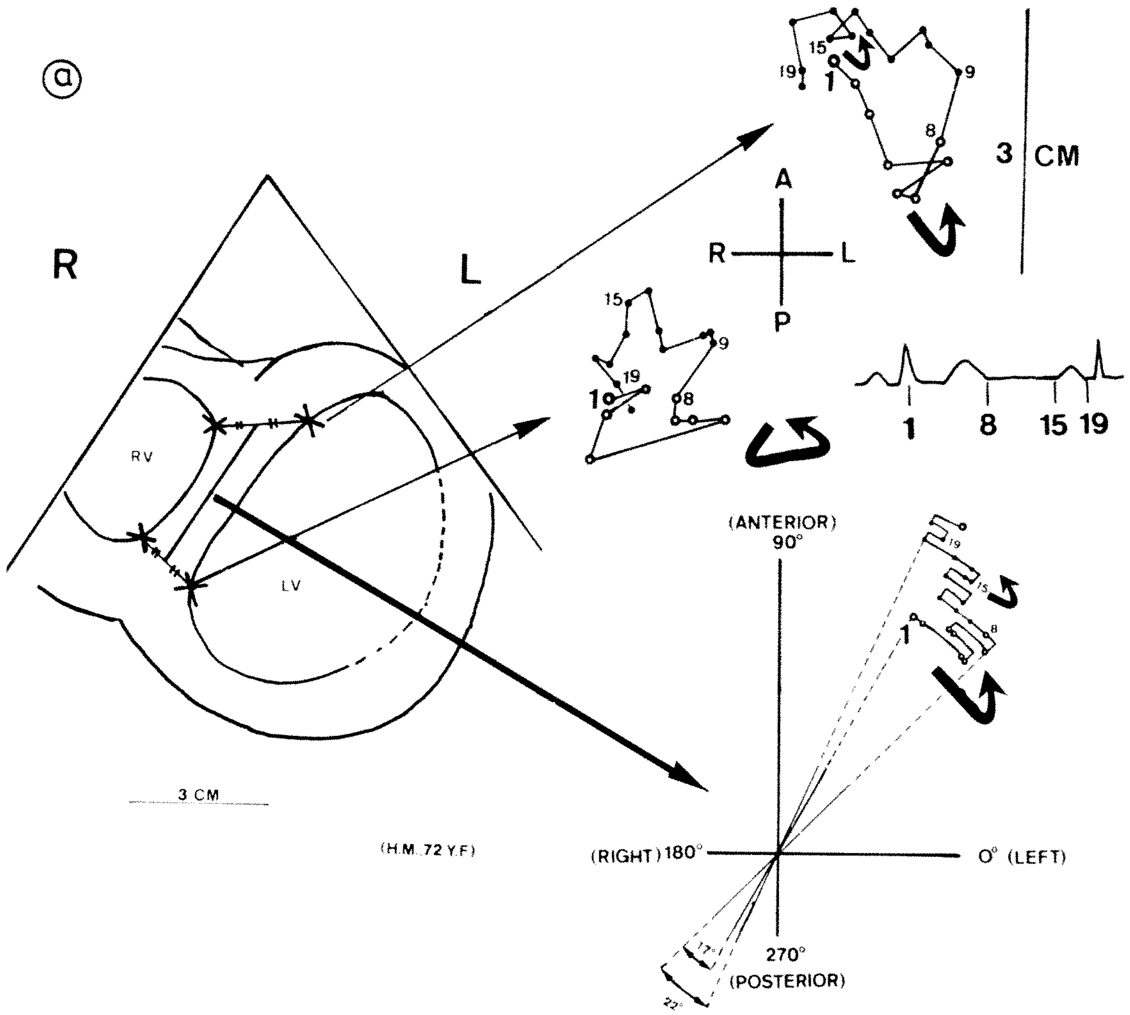
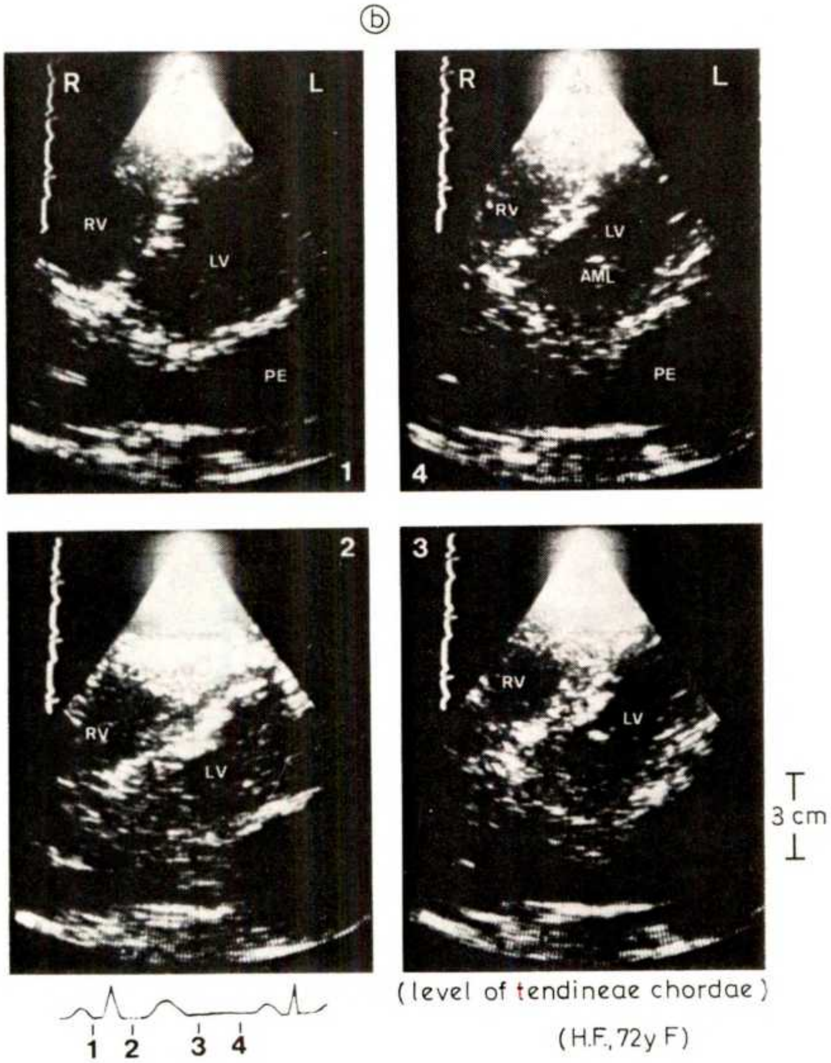


Fig. 5 *Evidence of cardiac twist and rotational excursion in horizontal cross-section at the level of interventricular septum.* (*a*) left panel: *schematic representation of a horizontal cross-section indicating points and angulation of the midline of the interventricular septum for tracings.* Right upper panel: *tracings of 2 points at the junction of the interventricular septum and left ventricular wall as indicated on the schematic cross-section of the heart in one cardiac cycle are shown. Open circles from 1 to 8 were in systole, solid circles from 9 to 19 were in diastole. Tracings of both points showed a large rotational excursion. The anterior point showed also counterclockwise triangular motion, which corresponded to twisting motion, during times 5 to 8 in systole and a sharp counterclockwise triangular motion during 14 to 17. The posterior point did not show twisting motion.* Right lower panel: *The successive angulation of the interventricular septum was measured and the angles were shown in polar co-ordinates. Changes in this angle indicate cardiac twist. Cardiac twists were frequently observed throughout the cardiac cycle, but 2 dominant deflections were noticed in mid to late systole, during times 4 to 8, and during atrial contraction, times 14 to 18.* (*b*) *Four representative frames of 20 cine frames used in tracing. The end of the electrocardiogram indicates the time of the image. AML, anterior mitral leaflet.*

associates (1966) made an attempt to document this rotational movement of the heart in electrical alternans in massive pericardial effusion by standard M-mode echocardiography. However, the rotational movement was not adequately shown by this technique since only anteroposterior movement was recorded by a single ultrasonic beam fixed in one direction. In 1971 Gabor *et al.* reported their echo-



cardiographic experience in pericardial effusion in which they had to introduce lateral swing of the heart in order to understand the electrocardiogram and echocardiographic observations of their patient. They discussed electrical and mechanical alternation in pericardial effusion from the viewpoint of standard echocardiography. In 1975 Matsuo *et al.* also suggested the presence of lateral swing of the heart in massive pericardial effusion based on the observation that the anteroposterior dimension of the left ventricle in mid-diastole was smaller than that in end-systole in the same echocardiographic cross-section along the long axis of the heart using the stop action technique.

Real-time visualisation of the heart has now become the method of choice of documenting the rotational excursion of the heart in massive pericardial effusion. The mechanism of distortion of the M-mode echocardiogram (Feigenbaum, 1976) has also been clarified by real-time observation of the heart in horizontal cross-sections. The quality of the images in this study recorded on Polaroid films with our prototype phased array echocardiograph is not totally satisfactory, but it has been much improved by altering the behaviour of the function of a logarithmic amplifier in the receiving circuit. Real-time observation and cine films exhibit cardiac structures clearly, for they display motion which

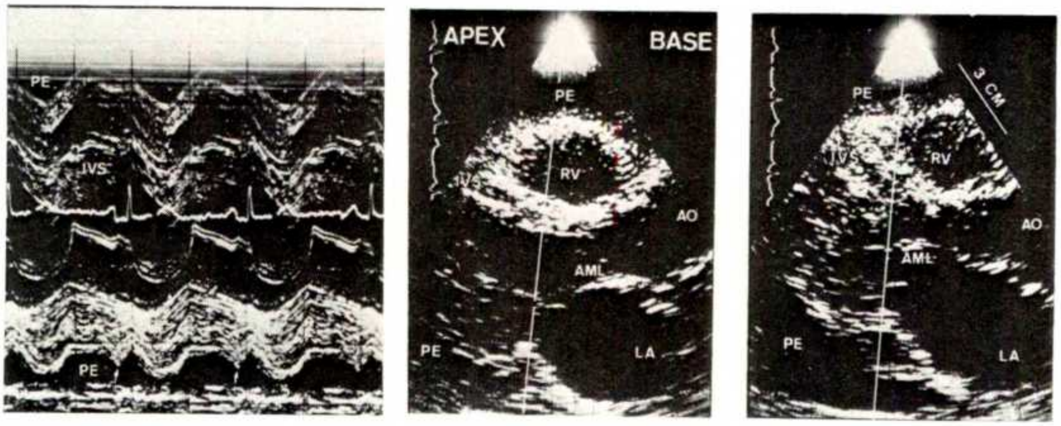


Fig. 6 *Anteroposterior swing motion in sections along the long axis of the heart.* Right panel: *a section in mid-diastole revealing the heart near the anterior chest wall.* Centre panel: *a section in mid-systole showing a posteriorly positioned heart.* Left panel: *a standard echocardiogram recorded with an ultrasound beam shown as a white line in the right and centre panels penetrating the right ventricle, interventricular septum, anterior mitral leaflet, and the atrioventricular junctional portion. This echocardiogram showed a posterior bowing pattern of the anterior mitral leaflet, mimicking the mitral valve prolapse, and a sharp downward triangular motion of the epicardium at the atrioventricular junctional portion. This seemed to correspond to the cardiac twist observed in horizontal sections and caused by atrial contraction. IVS, interventricular septum; AO, aorta; LA, left atrium.*

compensates for the low quality of individual images. The still Polaroid pictures exhibit an instant image which often appears poorer than real-time ones. This loss of quality is caused in part by side lobes, which lead to the appearance of ghost images and are difficult to prevent in phased-array echocardiography. Nevertheless, real-time cross-sectional echocardiography is useful for motion analysis of cardiac structures, and in the present study experimental error in tracings was avoided by maintaining two reference points at constant positions in each projection of the cine frames.

Yet to be established is the cause of this rotational excursion of the heart in massive pericardial effusion. The following factors seem responsible for this phenomenon: (i) removal of restraining influences of the pericardium together with that of the lungs and mediastinal structures on the natural rotational movement of the heart, (ii) spiral arrangement of the cardiac muscle, (iii) the asymmetry of ventricular contraction as described by McGregor and Baskind (1955) and Feigenbaum *et al.* (1966).

Large rotational excursion, especially in diastole, leads us to speculate that the difference in the type of blood inflow into both ventricles and/or dilatation of both ventricles may contribute to this phenomenon. The influence of heart rate (both the present cases showed slight bradycardia) must be considered. When heart rate increases to more than 100/minute, the shortening of diastole may limit the leftward and anterior excursion, leaving only the alternative, anteroposterior pendular motion. Feigenbaum speculated that production of rotational motion requires a large, chronically accumulated, and lubricant effusion (Feigenbaum, 1976).

The counterclockwise rotational movement of the heart in congenital or acquired absence of the pericardium, to which Payvandi and Kerber (1976) attributed the paradoxical motion of the interventricular septum in pericardial defect, is also interesting, for the heart is under an increased mobility, just as in the present cases of massive pericardial effusion.

The rotational excursion of the heart in massive pericardial effusion, which we have observed, seems to occur in the presence of the above factors. Cases of massive pericardial fluid may well be seen, however, which do not have this motion because of absence of some of the above-mentioned factors, or the presence of some restraining factor, such as adhesion, which would prevent the generation of this rotational excursion.

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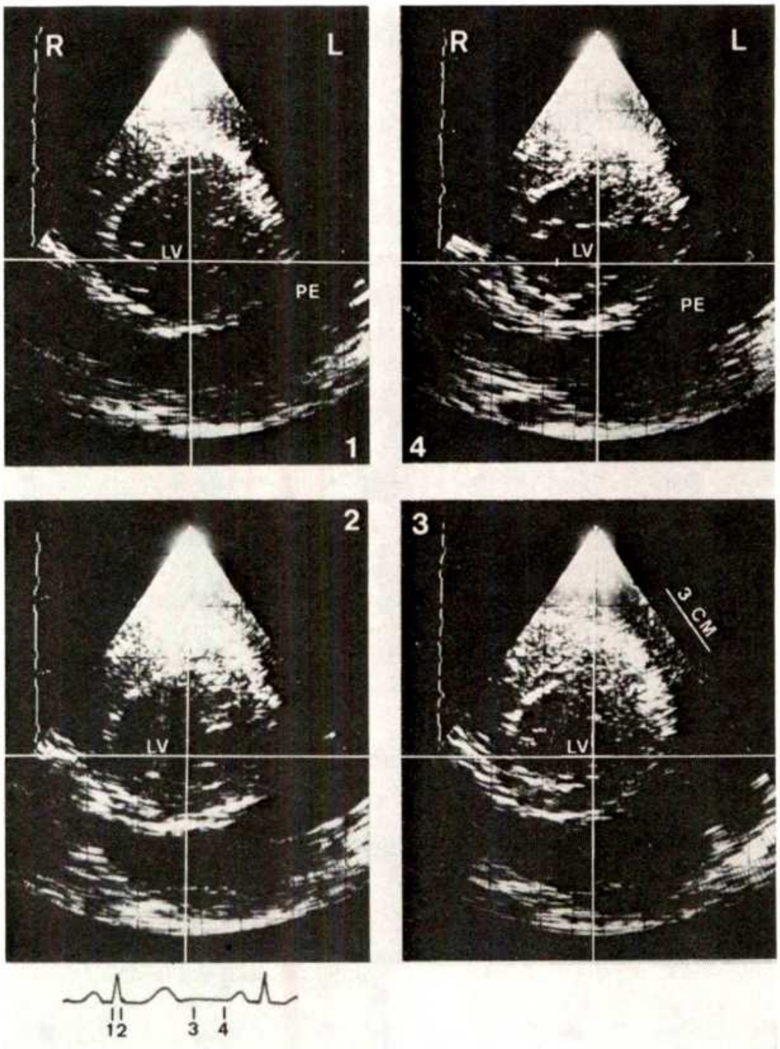

Fig. 7 *Rotational excursion and cardiac twist in horizontal cross-sections at the level of chordae tendineae of the mitral valve in case 2. Massive pericardial fluid was seen in this case, but excursion of the heart was not as large as in the first case. A slight localisation of the pericardial fluid was observed.*

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Evaluation of posterior aortic wall echogram in diagnosis of mitral valve disease

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SUMMARY The clinical usefulness of detecting abnormal movement of the posterior wall of the aortic root by M-mode echocardiography was studied in 93 patients with common cardiac diseases (mitral and aortic valve disease, atrial septal defect, hypertrophic and congestive cardiomyopathy) and in 17 normal subjects. Though abnormally slow ($<$ 3 cm/s) or prolonged ($>$ 240 ms) diastolic movement was confirmed to be common in mitral stenosis, since it occurred in 35 of 36 patients it was non-specific. Similar abnormalities frequently occurred in other patients with, for example, mitral regurgitation, aortic valve disease, after aortic valve replacement, and in both hypertrophic and congestive cardiomyopathy. The severity of mitral stenosis, assessed at operation, could not be accurately predicted from abnormalities of aortic root movement. Information derived from aortic movement was not diagnostic and did not predict severity in isolated mitral regurgitation though both the peak rate of systolic aortic motion and total aortic excursion were significantly greater than normal. We conclude that abnormalities of posterior aortic wall movement are frequent and their specificity and clinical usefulness are limited.

Attention was drawn to the movement of the aortic root as long ago as 1907 by Sir Arthur Keith, who realised that the most mobile part of the left atrium is its anterior wall, bordered by the aortic root. He argued from purely anatomical evidence that during left ventricular systole the aortic root would move forwards as the left atrium filled. Recent echocardiographic studies (Strunk *et al.*, 1976b, 1977; Akgün and Layton, 1977) have confirmed this prediction, that normal aortic root movement occurs mainly in response to left atrial volume changes, though the contributions of left ventricular ejection and elastic recoil of the aorta have yet to be defined (Pratt *et al.*, 1976).

More recently it has been postulated that aortic root movement is so closely related to left atrial volume changes that it can be used to predict the pattern of left ventricular filling in patients and hence the severity of mitral stenosis (Strunk *et al.*, 1977), the performance of mitral prostheses (Strunk *et al.*, 1977), the severity of mitral regurgitation (Strunk *et al.*, 1976a; Akgün and Layton, 1977), and the behaviour of the left ventricle itself in other unspecified conditions (Strunk *et al.*, 1976b).

The present study was designed to test these assertions by investigation of the types of abnormal posterior aortic wall movement occurring in several common forms of heart disease and to assess the specificity of such abnormalities.

Subjects and methods

Studies were made on 110 patients. There were 17 normal subjects ranging in age from 15 to 65 years. The diagnoses of the 93 patients with heart disease are shown in Table 1. These were confirmed in all patients with valve disease or atrial septal defect

Table 1 *Patients studied*

Diagnosis	*No. of patients*
Normal	17
Mitral stenosis	18
Severe non-rheumatic mitral regurgitation	15
Mixed mitral stenosis and regurgitation	12
Mixed aortic and mitral valve disease	6
Aortic regurgitation	10
Aortic stenosis	7
Previous aortic valve replacement	6
Atrial septal defect	6
Hypertrophic cardiomyopathy	6
Congestive cardiomyopathy	7

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at cardiac catheterisation or at operation. Of the 6 patients with hypertrophic cardiomyopathy, 4 were catheterised and the remaining 2 patients had typical clinical and echocardiographic findings with no evidence of aortic valve disease or hypertension. Three of the patients with congestive cardiomyopathy were not catheterised but had gross cardiomegaly, dilated poorly contracting left ventricles on echocardiography, and no evidence of ischaemic heart disease. No patients with ischaemic heart disease were included in the study.

ECHOCARDIOGRAMS

Echocardiograms were recorded at 75 or 100 mm/s paper speed using a Smith Kline Ekoline 20 ultrasonoscope connected to a Cambridge strip chart recorder, using a 2·25 MHz 1·25 cm transducer.

Data processing

Echocardiographic traces of both aorta and left ventricle were digitised as previously described (Gibson and Brown, 1973), using a Summagraphics digitiser (20 by 20 in, with 0·01 in resolution) and a Prime 300 computer system. Left ventricular and aortic traces were compared from beats of the same duration ± 75 ms and were recorded during the same session.

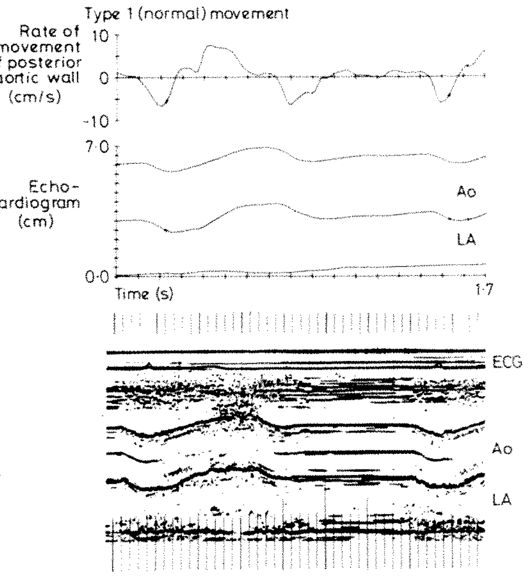


Fig. 1 *Echocardiogram of a normal subject and the derived data. From below upwards the traces represent the original echocardiogram, the digitised echocardiogram, and the rate of movement of the posterior aortic wall. This is type I movement. Crosses represent the timing of the onset of the QRS and aortic valve opening.*

(a) *Aortic root echocardiograms.* The leading edges of the anterior and posterior walls of the aortic root, and the posterior wall of the left atrium were digitised (Fig. 1). Traces of the aortic root were always taken so that some element of the aortic valve apparatus was included.

From these digitised traces the following data were calculated and plotted:

(i) Overall excursion of the posterior aortic wall during the cardiac cycle.

(ii) The amplitude of passive backward movement of the aorta; that is that occurring in early and mid-diastole, preceding the onset of atrial or ventricular systole.

(iii) The peak rates of early diastolic backward movement and systolic forward movement.

(iv) The duration of passive diastolic backward movement.

(v) The atrial emptying index (Strunk *et al.*, 1977). This measurement is the proportion of passive diastolic backward movement of the posterior aortic wall that occurs during the first third of diastole. Diastole, for this purpose, is taken as the period from the onset of backward aortic movement until the posterior aortic wall is deflected by atrial systole or ventricular systole; if neither deflect the aortic root, the end of the QRS marks the end of diastole. The left atrial dimension throughout the cardiac cycle was also plotted. Changes in this variable always followed posterior aortic wall excursion and therefore have not been tabulated.

(b) *Left ventricular echocardiograms.* Left ventricular echocardiograms showed clear continuous echoes of the left side of the septum and the endocardium of posterior wall. These traces were digitised and the instantaneous dimension and rate of change of dimension were plotted (Gibson and Brown, 1973). The peak rate of change of left ventricular dimension during systole and diastole was measured.

STATISTICS

Differences between groups were examined using unpaired t tests, and correlations between variables were examined using least squares linear regression. Values which differed from the mean of the normal group by more than 2 standard deviations were taken as being abnormal.

Results

PATTERN AND RATE OF AORTIC ROOT MOVEMENT

All normal subjects showed a similar pattern of aortic root movement. The total excursion was

Table 2 *Results from digitised aortic and left ventricular echocardiograms of 110 patients*

	Normal	*Mitral stenosis*	*Severe mitral regurgitation*	*Mixed mitral stenosis and regurgitation*	*Mitral and aortic v disease*
Total aortic excursion (mm)	9·2 ± 2·0	9·1 ± 3·4	12 ± 3·5*	8·0 ± 1·7	10·6 ± 3·1
Passive aortic excursion (mm)	6·3 ± 1·6	6·1 ± 2·5	8·3 ± 4·6	6·3 ± 2·4	3·3 ± 3·1*
Peak rate of aortic forward motion (cm/s)	4·9 ± 1·6	4·1 ± 1·7	6·5 ± 2·7*	3·9 ± 1·7	4·6 ± 1·9
Peak rate early diastolic backward movement of Ao (cm/s)	6·3 ± 1·6	2·9 ± 1·7***	5·6 ± 3·8	3·3 ± 2·0***	1·5 ± 3·8***
Peak rate LV diastolic dimension change (cm/s)	15·7 ± 2·8	6·3 ± 1·2*	33 ± 10*	16·1 ± 5·1	9·2 ± 2·9*
No.	17	18	15	12	6

All results = mean ± SD. *P < 0·05, ***P < 0·001.

9·2 ± 2·0 mm (mean ± SD) of which 6·3 ± 1·6 mm (mean ± 1 SD) occurred passively during diastole and the remainder in atrial or ventricular systole (Table 2). Diastolic movement was in a backward direction and occurred rapidly at first with a peak rate of 6·3 ± 1·6 cm/s, and then more slowly until the onset of atrial systole. The duration of this initial rapid phase was 160 ± 41 ms. On the basis of these normal results, termed type I (Fig. 1), 2 further patterns of movement were defined (Fig. 2). In type II (Fig. 3), the peak rate of early diastolic movement was reduced to less than 3 cm/s and its duration prolonged to more than 240 ms. In type III, duration was also prolonged but the peak rate was normal.

In 17 of the 18 patients with pure mitral stenosis the duration of the period of early diastolic backward movement was prolonged. In 13 of these the peak velocity of backward movement was reduced to below 3 cm/s. In 1 patient with significant mitral stenosis confirmed at catheterisation and operation, aortic root movement was normal. Similar abnormalities were also seen in mixed mitral valve disease whether accompanied by aortic valve disease or not. In 35 of the 36 patients

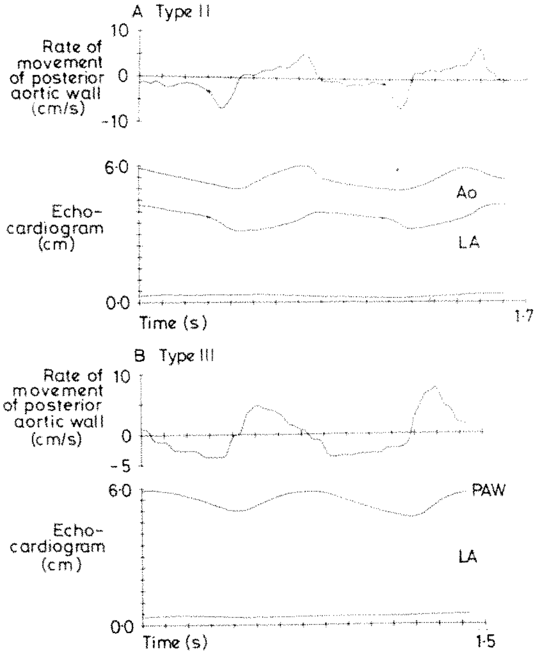


Fig. 2 *Echocardiographic data showing type II (derived from a patient with mitral stenosis) and type III aortic movement (from a patient after aortic valve replacement). The cross on the type II trace represents the onset of the QRS.*

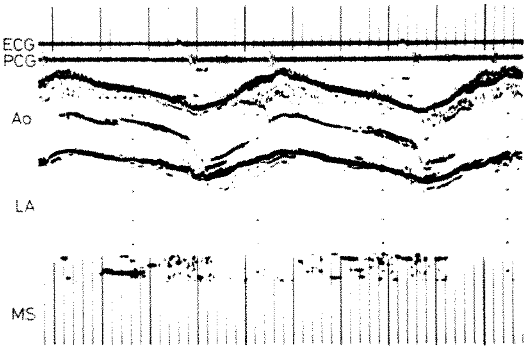


Fig. 3 *The echocardiogram of the aortic root in a patient with pure mitral stenosis. This is type II motion (peak rate of backward aortic root motion = 2·9 cm/s). The valve area at operation was 0·5 cm².*

rtic regurgitation	Aortic stenosis	Aortic valve replacement	Atrial septal defect	Hypertrophic cardiomyopathy	Congestive cardiomyopathy
9 ± 2·8	7·9 ± 2·9	10·5 ± 4·8	12·4 ± 3·6*	8·5 ± 2·9	8·6 ± 3·2
2 ± 3·8	4·4 ± 1·3*	9 ± 3·3	5·6 ± 2·9	6·2 ± 2·4	4·3 ± 3·1
6 ± 1·6	4·9 ± 1·5	3·8 ± 1·0	6·4 ± 2·4	4·7 ± 2·2	4·9 ± 2·9
8 ± 1·9*	3·2 ± 1·3***	2·8 ± 0·7	6·0 ± 3·6	4·3 ± 2·4	4·3 ± 2·6
1 ± 5·0	14·1 ± 7·0	10·5 ± 4·8*	16·7 ± 7·4	13·7 ± 7·0	11 ± 3·6*
	7	6	6	6	7

in whom there was any significant mitral stenosis there was an abnormal pattern of an aortic root movement. In patients with severe non-rheumatic mitral regurgitation the pattern of diastolic aortic root movement was normal in 7 and indistinguishable from that occurring in patients with significant mitral stenosis in the remaining 8 (Table 3). Abnormalities of diastolic aortic root movement were not confined to patients with mitral valve disease, but were also seen in pure aortic stenosis or regurgitation, and after aortic valve replacement. They were also present in other types of heart disease, particularly in congestive and hypertrophic cardiomyopathy (Tables 2 and 3), or after aortic valve replacement.

Patients with atrial septal defect, and those with severe mitral regurgitation both showed a significant increase in the total excursion of the posterior aortic wall (Table 2), and in severe, pure mitral regurgitation the peak rate of systolic anterior motion of the aorta was also significantly increased ($P < 0{\cdot}01$).

LEFT ATRIAL EMPTYING INDEX

The normal value for this variable was 0·85 ± 0·17 (mean ± 1 SD). In 11 of the 18 patients with pure mitral stenosis, values were abnormally low but in the remaining 7 were normal. (An abnormally low value was taken as more than 2 standard deviations less than normal, that is less than 0·5.) In 10 of these patients, the mitral valve area was measured directly at operation and found to be between 0·5 and 1 cm^2; but only 6 of these had a left atrial emptying index of less than 0·5 while in the remainder the atrial emptying index fell within our normal range. There was no correlation between mitral valve area and the atrial emptying index. Furthermore, in patients with atrial fibrillation, the left atrial emptying index often depended on the RR interval; values of atrial emptying index at different heart rates for 2 representative patients are plotted in Fig. 4. Abnormally low values of atrial emptying index often occurred in other conditions (Table 3), particularly in patients with cardiomyopathy and after aortic valve replacement.

Table 3 *Type of aortic movement occurring in all 110 patients*

	Normal	Mitral stenosis	Severe mitral regurgitation	Mixed mitral stenosis and regurgitation	Mitral and aortic valve disease	Aortic regurgitation	Aortic stenosis	Aortic valve replacement	Atrial septal defect	Hypertrophic cardiomyopathy	Congestive cardiomyopathy
Number	17	18	15	12	6	10	7	6	6	6	7
Atrial emptying index < 0·5	1	11	6	7	6	6	3	5	2	5	6
Type I	17	1*	7	—	—	5	4	1	5	1	4
Type II	—	13	2	8	2	2	2	2	—	3	2
Type III	—	4	6	4	4	3	1	3	1	2	1

*Only patient with mitral stenosis and a normal pattern of aortic movement.

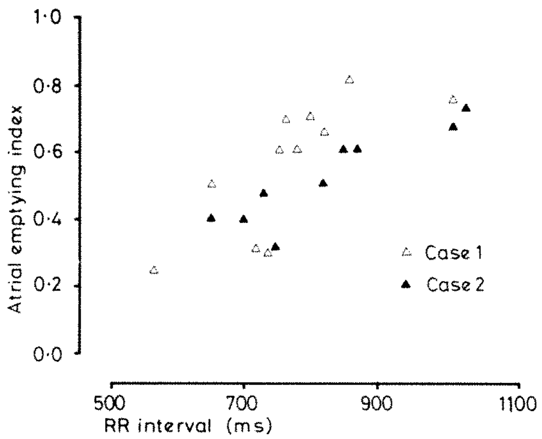
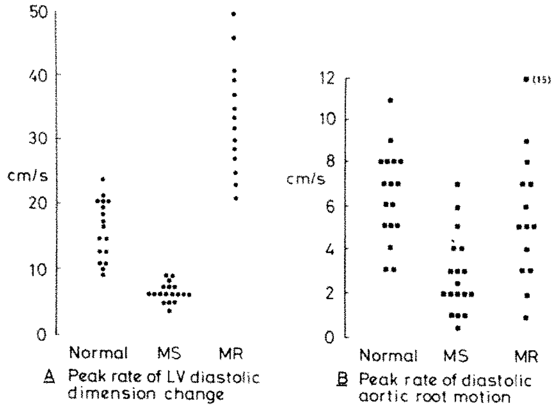


Fig. 4 *The variation of the atrial emptying index with RR interval in 2 patients with atrial fibrillation and moderately severe mitral stenosis.*

PEAK RATE OF LEFT VENTRICULAR DIMENSION INCREASE

Values for peak diastolic rate of left ventricular dimension increase are given in Table 2 and shown diagrammatically in Fig. 5. It can be seen that most patients with mitral stenosis or mitral regurgitation could be separated both from normal and from each other on the basis of measurements of peak rate of increase in their left ventricular dimension, but not by the peak rate of early diastolic aortic root movement (Fig. 5), total aortic root excursion, or atrial emptying index. Attempts to normalise the values of any of these aortic variables for left atrial size did not improve agreement. There was no linear correlation between peak rates of change of left ventricular dimension in diastole and the rate of diastolic aortic root movement, either when all patients were considered together or in separate diagnostic groups. In general, if left ventricular dimension change, measured echocardiographically, was slow (< 10 cm/s), then aortic root movement in diastole (Fig. 6) was also slow or prolonged (34 of 41 patients), but aortic root movement was often abnormal when the left ventricular echocardiogram was normal (31 of 52 patients).



A Peak rate of LV diastolic dimension change

B Peak rate of diastolic aortic root motion

Fig. 5 *Comparison of (A) peak rate of left ventricular dimension change and (B) peak rate of diastolic aortic root motion in patients with pure mitral stenosis (MS) or mitral regurgitation (MR) and normal subjects.*

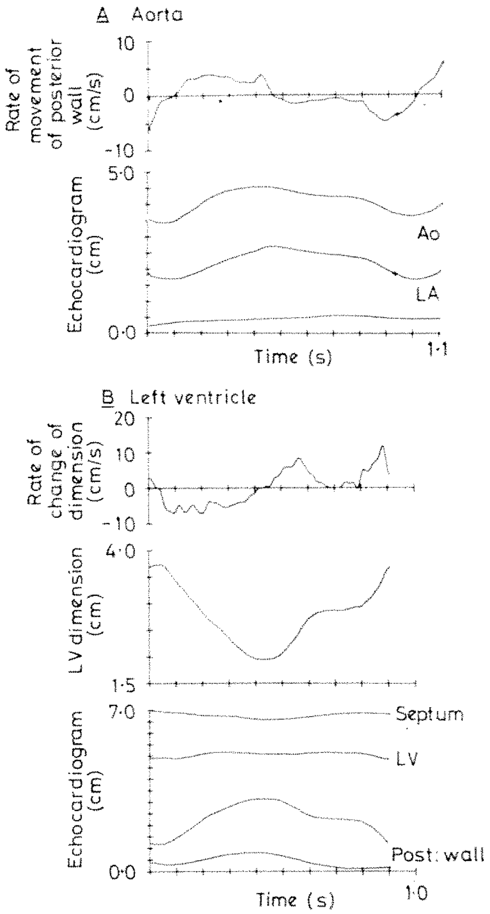


Fig. 6 *Echocardiographic tracings and derived data of left ventricle and aorta in a patient with severe aortic stenosis. This shows type II movement and slow left ventricular dimension change. From below upwards the tracings are as follows: left ventricular echocardiogram, left ventricular dimension, rate of left ventricular dimension change, aortic echocardiogram, rate of movement of posterior aortic wall.*

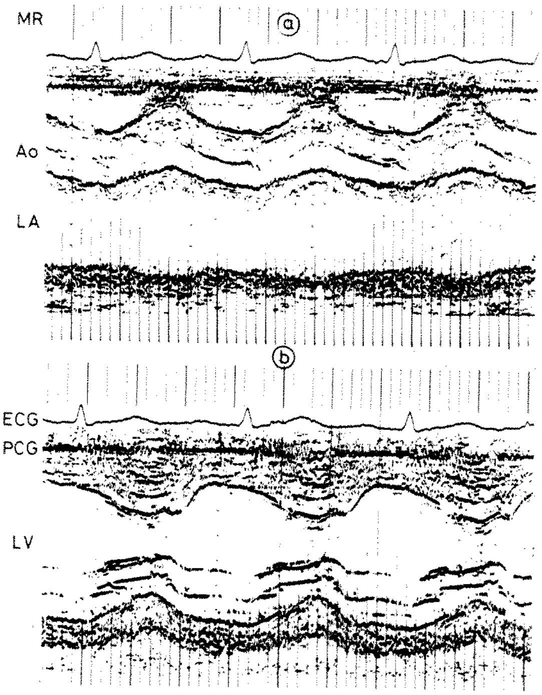


Fig. 7 *The aortic and left ventricular echocardiograms from a patient with severe mitral regurgitation. Left ventricular filling is rapid (peak rate of left ventricular diastolic dimension change 25 cm/s, upper limit of normal 21·3 cm/s) but the peak rate of aortic root motion is 3·5 cm/s and the duration of movement is increased (360 ms). This is type III motion. PCG, phonocardiogram.*

Discussion

The present study has confirmed previous ones in showing that the posterior wall of the aortic root moves in a way that might be predicted from the left atrial volume curve, and that abnormal patterns may occur in patients with heart disease. We were, however, unable to confirm that these abnormalities were specific to particular conditions or physiological disturbances, or that they were of value in the assessment of individual patients.

Two separate approaches to the quantification of aortic root movement have been used. The first, the left atrial emptying index, was described by Strunk *et al.* (1977), and found by them to correlate well with the mitral valve area, corrected for body surface area, in 25 patients with mitral stenosis. These authors also suggested that the atrial emptying index might provide useful information about prosthetic mitral valve dysfunction. We were not able to confirm these results. Though in the majority of patients with mitral stenosis, atrial emptying index was reduced, it was not possible to use it to predict the mitral valve area found at operation with any accuracy, and in 4 patients with severe narrowing this index was only slightly reduced or even normal. Its dependence on heart rate must introduce uncertainty into any attempt to use it in assessing patients with mitral stenosis and atrial fibrillation. Its value in detecting possible prosthetic valve dysfunction was not formally investigated in the present study, but the frequent appearance of abnormal aortic root movement after cardiac operations not involving the mitral valve did not encourage us to pursue its use in this direction.

A second approach was defined by Akgün and Layton (1977) who suggested that echocardiographic measurement of left atrial dimension change might help in assessing the severity of mitral regurgitation. We were able to confirm that left atrial dimension change assessed by measuring total excursion of the posterior aortic wall, which is the only mobile wall of the left atrium, is increased in mitral regurgitation and that forward aortic movement in systole is abnormally rapid.

These changes could not be used, however, to diagnose mitral regurgitation since aortic root excursion was also increased in patients with atrial septal defect, nor could they be used to define the severity of mitral regurgitation since they were not present in 8 of the 15 patients. The inability of early diastolic aortic root movement accurately to predict left ventricular filling rates is highlighted by the findings in mitral regurgitation. In 14 of 15 patients with severe mitral regurgitation the left ventricular filling rate measured as the peak rate of diastolic left ventricular dimension change was abnormally rapid (more than 2 standard deviations greater than normal, that is $> 21{\cdot}3$ cm/s) but in 12 of these 14 patients the peak rate of early diastolic aortic root motion was normal (Fig. 7) or less than normal ($< 9{\cdot}5$ cm/s).

A reduction in the peak rate of early diastolic aortic root motion (type II motion) was a sensitive (present in 13 of 18 patients) but non-specific indicator of pure mitrals tenosis, since though it occurred most commonly in pure mitral stenosis it was also seen in 2 patients with pure mitral regurgitation, as well as in patients with aortic valve disease, after aortic valve replacement, and with congestive or hypertrophic cardiomyopathy. The ability to detect mitral stenosis from aortic root motion was increased further by considering type III motion (prolonged diastolic backward motion occurring at a normal rate), since 17 of the

18 patients with mitral stenosis had either type II or III motion. Though considering both types of motion increased sensitivity it also reduced specificity further since many other patients without mitral valve disease showed type III motion.

Measurements of peak rates of diastolic aortic root movement also performed much less well than those of transverse left ventricular dimension in separating patients with mitral stenosis or regurgitation from normal (Fig. 5). The theoretical possibility that measurement of posterior aortic root movement might be of value in excluding mitral stenosis in circumstances when other echocardiographic measurements could not be obtained for technical reasons was not found to apply, since a recognisable mitral valve echogram was recorded in all, and, though we failed to obtain satisfactory left ventricular echograms in 7 patients, aortic root measurements were not possible in 5 other patients.

The pathophysiological basis of this lack of specificity of aortic root movement seems clear. The amplitude and rate of this movement during the cardiac cycle must depend on the relative rates of left atrial inflow and outflow of blood, the size and distensibility of the left atrium, and the mobility of the aortic root. The left atrium has 5 large openings in its walls, only 1 of which has a valve; it is frequently enlarged in heart disease and the properties of its walls may be altered by many factors including rheumatic disease, fibrosis, mural thrombus, and scarring from previous operations. The mobility of the aortic root must also be affected by fibrosis, scarring, and calcification both in it and in the adjacent mitral valve and left atrium. Therefore, it is not surprising that movement of the posterior aortic wall should be altered in such a non-specific and unpredictable way in heart disease.

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Determination of pressure gradient in mitral stenosis with Doppler echocardiography

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SUMMARY The accuracy of a non-invasive ultrasound Doppler technique for the determination of the pressure gradient in mitral stenosis was evaluated in a study of 8 adult patients. Transseptal left atrial catheterisation and retrograde left ventricular catheterisation were performed. The same diastoles were used to compare the gradient constructed from the ultrasound data ($\triangle P_U$) with that constructed from the manometric data ($\triangle P_M$). In the 8 patients the difference between the mean diastolic values of $\triangle P_U$ and $\triangle P_M$ was − 0·54 ± 1·0 (SD) mmHg. The corresponding figure for mid-diastole was 0·01 ± 0·9 (SD) mmHg. The results indicate that the ultrasound technique is sufficiently accurate for diagnostic purposes.

In an initial study of a non-invasive ultrasound Doppler technique for the determination of the pressure gradient in mitral stenosis (Holen *et al.*, 1976) it was found that ultrasound can consistently register the frequency shifts from the diastolic mitral jet, and that the pressure gradient determined with ultrasound ($\triangle P_U$) agrees reasonably well with the manometric gradient ($\triangle P_M$) obtained from the pulmonary capillary venous and left ventricular pressures. Subsequent ultrasound studies of more than 150 patients with mitral stenosis have reinforced this impression.

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The present investigation was undertaken to explore the accuracy of the technique more closely by comparing $\triangle P_U$ with the manometric gradient obtained from left atrial (transseptal) and left ventricular pressures.

Subjects and methods

Data were collected from 8 adult patients undergoing routine preoperative cardiac catheterisation for mitral valve disease (Table).

ULTRASOUND SYSTEM

The frequency shifts from the mitral jet were

Table *Data and numerical results on cases (gradients rounded off to nearest mmHg)*

Case no.	*Age*	*Sex*	*HR*	*R*	$\dot{Q}$	*Valve lesion*	*Gradients (mmHg)*			
							Mean diastolic		*Mid-diastolic*	
							$\triangle P_U$	$\triangle P_M$	$\triangle P_U$	$\triangle P_M$
1	66	F	90	AF	3·1	MS, MR	14	14	15	15
2	52	M	68	SR	4·2	MS, MR, AR	7	8	8	8
3	54	M	64	SR	4·4	MS	11	13	10	11
4	66	F	58	SR	8·0	MS	4	5	3	5
5	46	F	60	AF	—	MS	13	13	11	11
6	66	F	76	AF	3·4	MS	9	8	9	9
7	30	M	86	AF	7·7	MS	13	13	13	12
8	56	M	70	SR	8·0	MS	11	12	9	9
$\bar{X}$	55		72		5·6		10·3	10·8	9·8	10·0
SD	11		12		2·3		3·5	3·3	3·7	3·0

HR, heart rate; R, rhythm; $\dot{Q}$, cardiac output (l/min); $\triangle P_U$, gradient from ultrasound data; $\triangle P_M$, gradient from manometric data; MS, mitral stenosis; MR, mitral regurgitation; AR, aortic regurgitation; SR, sinus rhythm; AF, atrial fibrillation; $\bar{X}$, mean value; and SD, standard deviation.

obtained with a modified (Holen *et al.*, 1976) 2·1 MHz continuous waveform Hewlett-Packard 8026B Sound Monitor. The ultrasound data were recorded on magnetic tape and subsequently frequency-analysed on a Kay Sona-Graph 6061B Sound Spectrum Analyzer. The hard copy of the frequency analysis is a grey scaled presentation wherein the abscissa is time and the ordinate frequency shift (Fig. 1b-4b). The degree of blackening at any particular point in the frequency analysis is in theory related to the energy present in the reflected sound, but electronic noise can also produce blackening. In the present investigation frequency analysis of the obtained Doppler spectrum was performed so that the time course of the maximum diastolic frequency shift ($\triangle f_{max}$) could be identified. In the frequency analysis $\triangle f_{max}$ is a curve drawn to envelop the blackening caused by the diastolic blood velocities. In order to identify $\triangle f_{max}$ as accurately as possible it is important that there is ample contrast between blackening from blood velocities and blackening from electronic noise. This contrast is in part dependent upon instrumentation, instrument settings, and ultrasound probe position.

MANOMETRIC SYSTEM

Left atrial and left ventricular pressures were obtained via 8F catheters. The catheters were connected to EMT-34 transducers (Elema Schönander) and pressures recorded by a Mingograph system.

COLLECTION OF DATA

The ultrasound and manometric data were collected simultaneously with the patient resting in the supine position. Immediately before the collection of data the optimum probe position on the patient's left anterior or lateral chest wall was identified with the aid of the audio signal of the Doppler spectrum (the optimum probe position is defined as that in which the incident sound beam is in acoustic contact with the diastolic mitral jet with its axis as closely aligned with the direction of the vectors with maximum diastolic velocity as is possible). This was accomplished by identifying the probe position where the audio signal of the diastolic Doppler spectrum seemed to contain the largest amount of high frequency sound. With the probe in the optimum position the ultrasound and manometric data were recorded simultaneously, provision being made for the identification of individual cardiac cycles in both so that the results from individual diastoles could be compared.

CONSTRUCTION OF GRADIENTS FROM ULTRASOUND AND MANOMETRIC DATA

The construction of the diastolic time course of the gradient from the ultrasound data was based upon three assumptions:

(1) The registered time course of $\triangle f_{max}$ reflected the maximum blood velocities in the mitral orifice.

(2) The probe position during data collection was such that the axis of the incident sound beam coincided with the direction of the vectors with maximum velocity in the orifice, thus allowing $\cos\theta = 1$ in the Doppler equation (Kinsler and Frey, 1962),

$$V_{max} = \frac{c \cdot \triangle f_{max}}{2 \cdot f \cdot \cos\theta} \quad \text{Doppler equation} \qquad 1$$

Where, V_{max} = maximum blood velocity, c = velocity of sound in blood, $\triangle f_{max}$ = maximum frequency shift, f = frequency of incident sound beam, and θ = angle between axis of incident sound beam and direction of vectors with maximum blood velocity.

(3) The steady state orifice equation (eq. 2) (Streeter, 1961) is valid for the flow in stenotic mitral orifices

$$\triangle P = \tfrac{1}{2}\rho\,(V_{max})^2 \quad \text{Orifice equation} \qquad 2$$

where $\triangle P$ = pressure gradient, ρ = mass density of blood, and V_{max} = maximum blood velocity.

$$\text{Thus, } \triangle P = \tfrac{1}{2}\rho\left[\frac{c \cdot \triangle f_{max}}{2 \cdot f \cdot \cos\theta}\right]^2$$

$$\text{And } \triangle P = \tfrac{1}{2}\rho\left[\frac{c^2}{2^2 \cdot f^2 \cdot \cos^2\theta}\right] \cdot \triangle f_{max}^2$$

Using $c = 1{\cdot}57 \cdot 10^5$ cm/s (Hertz, 1977), $f = 2{\cdot}1 \cdot 10^6$ Hz, $\cos\theta = 1$, and $\rho = 1{\cdot}06/981$ g s² per cm⁴ (Diem and Lentner, 1962) and using 1·36 for mmHg conversion yields the following working equation

$$\triangle P = \frac{1}{1{\cdot}36} \cdot \frac{1}{2} \cdot \frac{1{\cdot}06}{981}\left[\frac{1{\cdot}57^2 \cdot 10^{10}}{2^2 \cdot 2{\cdot}1^2 \cdot 10^{12}}\right] \cdot \triangle f_{max}^2 \cdot 10^6$$

$$\text{or } \triangle P_U = 0{\cdot}55 \cdot \triangle f_{max}^2 \qquad 3$$

where $\triangle P_U$ = pressure gradient determined from ultrasound data (mmHg) and $\triangle f_{max}$ = maximum diastolic frequency shift (kHz).

The time course of $\triangle f_{max}$ was drawn by hand on the hard copy of the frequency analysis as a curve enveloping the blackened areas representing diastolic blood velocities. The time course of $\triangle P_U$ was then constructed from $\triangle f_{max}$ using eq. 3. The time course of the manometric gradient ($\triangle P_M$) was constructed from the values obtained by subtracting the left ventricular diastolic pressure from the left atrial diastolic pressure.

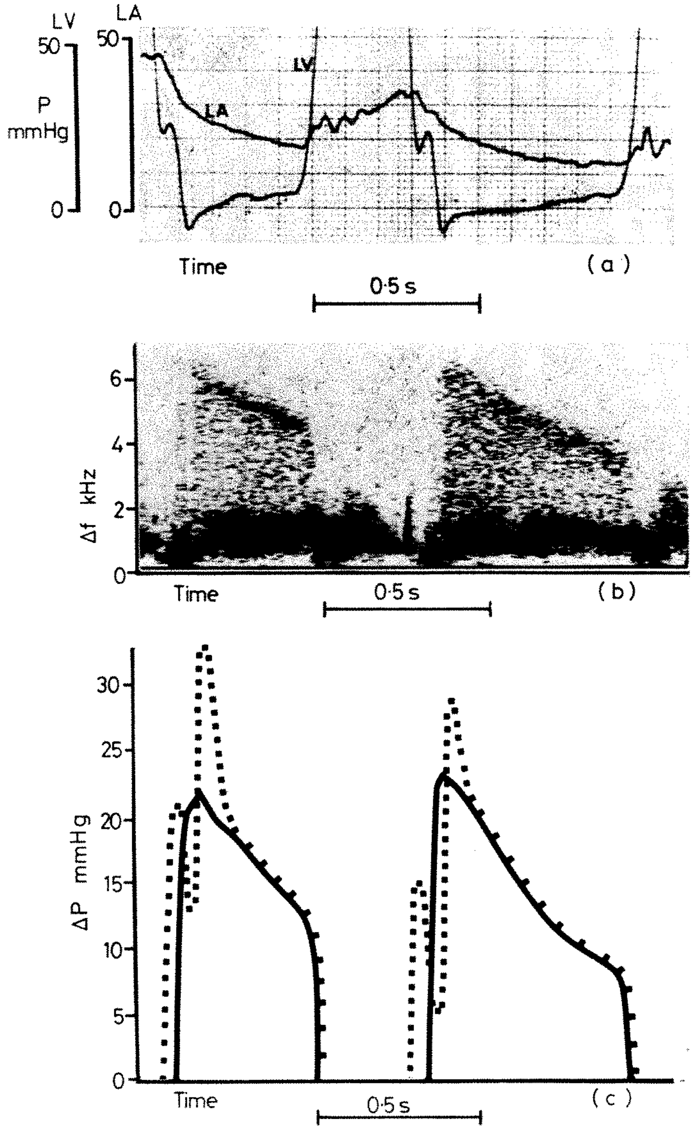

Fig. 1 *Two consecutive diastolic periods (atrial fibrillation) from case 1. (a) Pressure tracings. P, pressure; LV, left ventricle; LA, left atrium. (b) Frequency analysis. $\triangle f$, frequency shift. A hypothetical curve enveloping blackened diastolic areas will represent time course of maximum diastolic frequency shift. Note blackened band of about 0·5 kHz width adjacent to maximum frequency shift (most prominent in the first diastolic period). (c) Constructed gradients. $\triangle P$, pressure gradient; ——, gradient from ultrasound data; - - -, gradient from manometric data.*

COMPARISON OF $\triangle P_U$ AND $\triangle P_M$

In general gradients were constructed from 3 to 4 consecutive diastolic periods in each patient. Comparisons were made of the mean diastolic and the mid-diastolic values of $\triangle P_U$ and $\triangle P_M$.

Results

Representative pressure recordings, frequency analyses, and constructed gradients are presented in Fig. 1 to 4. In any given patient there was minimal variation in the quality of the recordings. A total of 28 diastolic periods were analysed and the gradients constructed.

The curve representing $\triangle f_{max}$ was drawn by hand as a line demarcating the relatively heavy blackening caused by blood velocities from the lighter blackening produced by electronic noise. With the exception of the extremes of diastole the accuracy with which the location of $\triangle f_{max}$ could be determined was estimated as ± 1/8 (SD) kHz. According to eq. 3 this corresponds to ± 0·4 (SD),

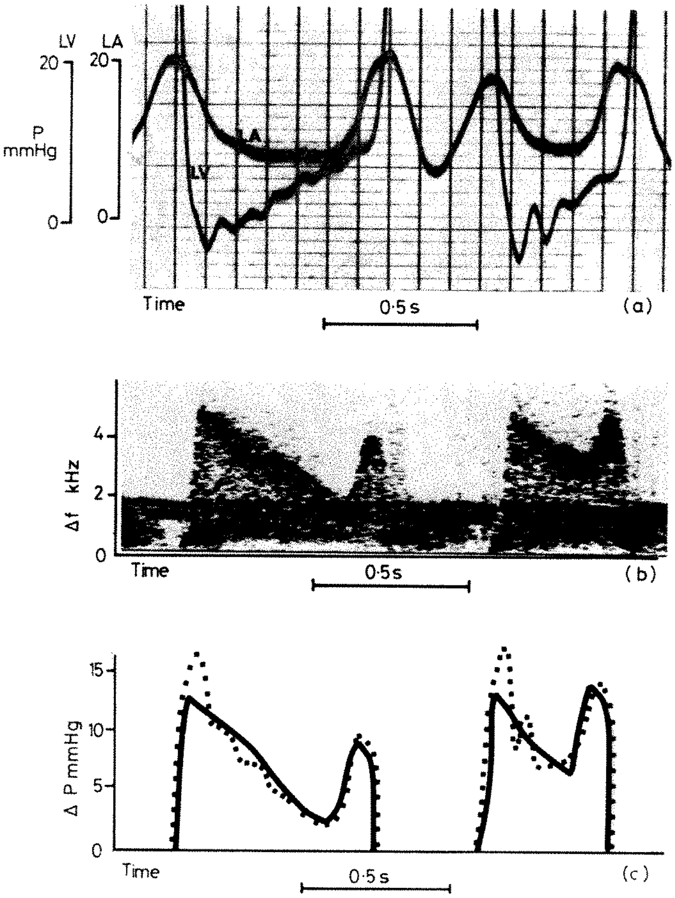

Fig. 2 *Consecutive diastolic periods (sinus rhythm) from case 2. (a) Pressure tracings. (b) Frequency analysis. Blackened band of about 0·75 kHz width at 2 kHz is caused by extraneous interference. Note effect of atrial contraction in late diastole. (c) Constructed gradients. Symbols as in Fig. 1.*

± 0·6 (SD), ± 0·7 (SD), and ± 0·8 (SD) mmHg for gradients of 5, 10, 15, and 20 mmHg, respectively. Near the extremes of diastole where Δf_{max} was less than 2 kHz the frequency shifts caused by the mitral jet were obscured in some patients by blackening from valve motion and ventricular blood velocities. In these regions Δf_{max} was drawn as a straight line continuation of the definable part of the curve.

The rate of change with time of Δf_{max} was greatest immediately after the onset of diastolic flow and immediately before its cessation. Relatively rapid changes in Δf_{max} also occurred during atrial contraction, whereas in general conditions approaching a steady state prevailed in mid-diastole (Fig. 1b to 4b).

With the exception of one patient (Fig. 4b), the frequency analyses exhibited a band of relatively heavy blackening adjacent to Δf_{max} in the mid-portion of diastole.

The left ventricular pressure tracings showed early diastolic oscillation in all patients (Fig. 1a to 4a) and the effect of this oscillation was prominent in the constructed time course of ΔP_M (Fig. 1c to 4c). Similar oscillation was not observed in the frequency analyses or in left atrial pressure tracings. In patients in sinus rhythm the effect of atrial contraction was distinctly shown in both ΔP_U and ΔP_M (Fig. 2c to 4c). In early diastole and during atrial contraction, peak ΔP_M invariably exceeded peak ΔP_U. The major discrepancies between ΔP_U and ΔP_M were found in association with these gradient peaks.

In the 8 patients the mean diastolic value of ΔP_M was 5 to 14 mmHg (Table). The difference between the mean diastolic value of ΔP_U and the mean diastolic value of ΔP_M was − 0·54 ± 1·0 (SD) mmHg. The corresponding value for the mid-diastolic gradients was 0·01 ± 0·9 (SD) mmHg.

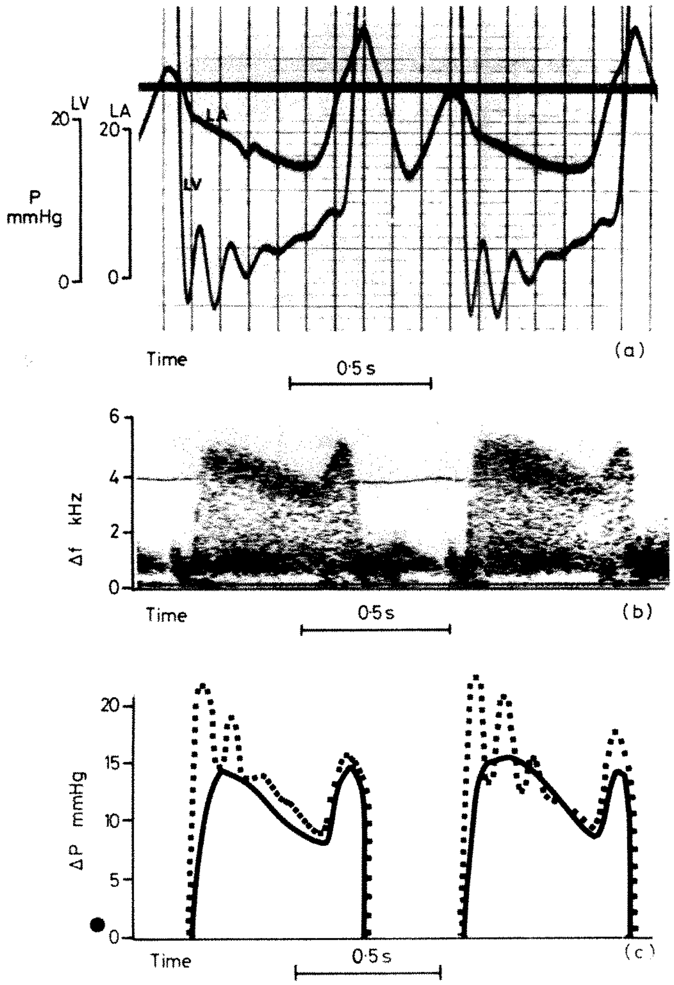

Fig. 3 *Consecutive diastolic periods from case 3. (a) Pressure tracings. Note oscillation in tracing from left ventricle. (b) Frequency analysis. (c) Constructed gradients. Symbols as in Fig. 1.*

Discussion

The liquid-filled catheters used in the manometric system are likely to produce significant errors in ΔP_M in the vicinity of the rapid pressure changes. The oscillation in the left ventricular pressure tracings supports this contention. Peak values and timing of ΔP_M therefore may well be erroneous.

The pressure gradient in mitral stenosis can be considered as the sum of an inertial and a dissipative (frictional loss) component. The steady state orifice equation (eq. 2) neglects the inertial component; thus ΔP_U will also misrepresent the actual gradient during rapid pressure changes and this can be expected to influence the value of the mean diastolic gradient more than the mid-diastolic one. The finding that agreement between mid-diastolic values of ΔP_U and ΔP_M was slightly better than that between mean diastolic values may reflect this; alternatively, it is possible that the difference in agreement is chiefly the result of errors in ΔP_M. In any event it appears that neglect of the inertial component of the gradient has only a minimal influence on the agreement between the mean diastolic values of ΔP_U and ΔP_M.

The orifice equation also neglects frictional losses incurred upstream of the flow sector where blood velocity is at its maximum. The mid-diastolic agree-

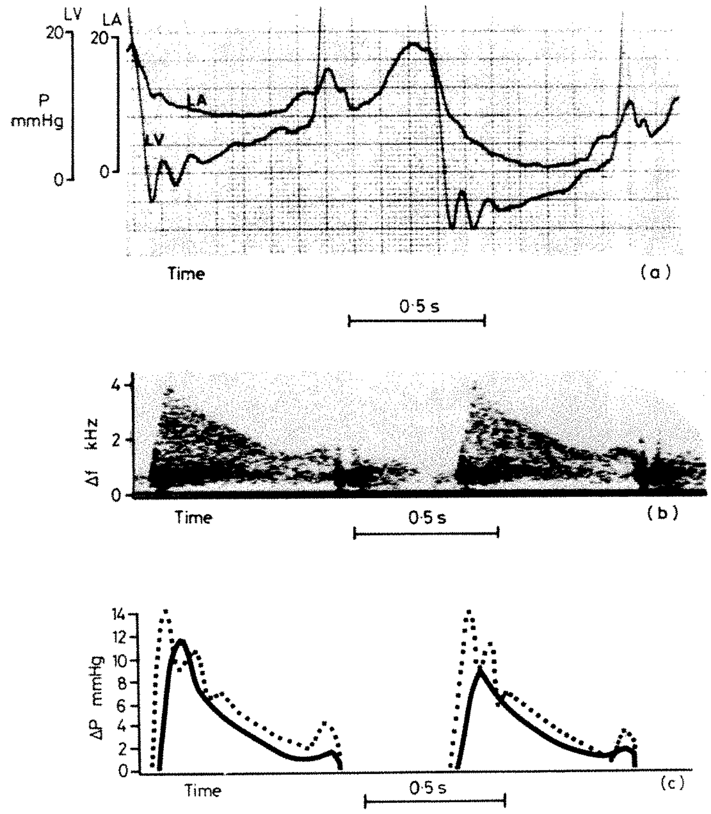

Fig. 4 *Consecutive diastolic periods from case 4. (a) Pressure tracings. (b) Frequency analysis. (c) Constructed gradients. Symbols as in Fig. 1.*

ment found between $\triangle P_U$ and $\triangle P_M$ indicates, however, that the equation predicts the dissipative component of the pressure gradient with reasonable accuracy. This conclusion is supported by the results of previously described *in vitro* studies of the equation (Holen *et al.*, 1977).

Failure to achieve a probe position where the axis of the incident sound beam coincides with the direction of the vectors with maximum velocity can theoretically lead to a major underestimation of the actual pressure gradient (eq. 1). The confidence that can be placed in the ultrasound technique is undoubtedly enhanced if satisfactory probe positioning can be confirmed by inspection of the frequency analyses, for previous experience with the technique has indicated that the blackened band adjacent to $\triangle f_{max}$ in the mid-portion of diastole is a sign of this. The band is believed to be the result of the incident sound beam traversing the left ventricle along the mitral jet and thus exposes a large volume of high velocity blood. Failure to achieve correct probe positioning may thus account for the relatively large mid-diastolic discrepancy between $\triangle P_U$ and $\triangle P_M$ found in case 4. Clearly, the effects of probe position on the appearance of the frequency analyses warrant further study.

Conclusions

(1) This ultrasound technique appears to determine mean and mid-diastolic mitral valve gradients with an accuracy that is sufficient for diagnostic purposes. (2) The accuracy of the technique is chiefly limited by the accuracy with which $\triangle f_{max}$ can be determined from the frequency analyses. (3) The orifice equation (eq. 2) predicts the dissipative component of the pressure gradient with an accuracy that is acceptable for diagnostic purposes. (4) Neglect of the inertial component of the pressure gradient influences the value of the mean gradient very little. (5) A satisfactory probe position ($\cos \theta = 1$ in eq. 1) can be attained in the majority of patients with mitral stenosis and can probably be confirmed by inspection of the frequency analyses.

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Echocardiography in cardiovascular drug assessment

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SUMMARY The validity of using echocardiography to measure the effects of cardiovascular drugs on the heart has been investigated. A standardised method of measuring left ventricular diameters is described and used to measure variability and therefore reproducibility in 20 subjects. Immediate variability was measured in 10 normal subjects. In 5 of these subjects variability was measured every few minutes, hourly, and weekly during control periods of drug studies and also after an interval of 1 year. Estimates were made of the minimum significant change in heart size which could be defined under these circumstances. Reproducibility decreased with increasing time interval between studies but overall was very good (coefficient of variation in diameters from 1 to 8%). Even with a time interval of 1 year the individual absolute difference in the mean of diameters was never greater than 0·3 cm. Reproducibility was similar in small groups of patients with hypertension or ischaemic heart disease (without dyskinesia).

Estimated sensitivity could be increased for any time interval equally as much by increasing the number of measurements on each occasion and modifying statistical analysis accordingly as by doubling the number of subjects. There was a fourfold difference between minimum and maximum sensitivity.

After 0·5 mg sublingual glyceryl trinitrate, diastolic and systolic diameters decreased significantly in all subjects. Estimated ventricular and stroke volumes were reduced. Cardiac output was unchanged as heart rate increased from 67 to 80 beats per minute while blood pressure fell. The estimated ejection phase indices (ejection fraction, fractional shortening, and fibre shortening rate) all increased significantly.

With rigid standardisation echocardiography could be a potentially useful non-invasive method of measuring the effects of cardiovascular drugs on the heart.

Echocardiography is well established as a useful non-invasive method of cardiac diagnosis. Echocardiographic estimates of left ventricular internal diameter and derived haemodynamic indices have correlated well with standard angiographic measurements (Fortuin *et al.*, 1971; Feigenbaum *et al.*, 1972; Murray *et al.*, 1972) and have therefore been used to assess left ventricular function (Fortuin *et al.*, 1972; Belenkie *et al.*, 1973). These methods make assumptions about the echocardiographic internal diameter and its relation to a geometric model of the left ventricle which may be questionable (Linhardt *et al.*, 1975) especially at the extremes of cardiac size or where there is dyskinesia (Teichholz *et al.*, 1976). It has, however, been suggested that echocardiographic estimation of ventricular function is still suitable for the sequential study of individuals and has been proposed as a suitable method of measuring the effects of cardiovascular drug action on the heart (Gibson, 1973; Hirshleifer *et al.*, 1975). Though the ability of echocardiography to measure drug-induced changes in heart size in certain circumstances appears to have been shown (Redwood *et al.*, 1974), in most studies the drug-induced changes were small and where assessed have not necessarily correlated with other measures of cardiovascular drug action (Frishman *et al.*, 1975). Conversely, relatively large changes have not always been significant (Seabra-Gomes *et al.*, 1976).

The ability of echocardiography to measure drug-induced changes in heart size accurately depends in part on the sequential variation in echocardiographic diameters during repeated control measurements. Previous measurement of this variation has produced differing results (Pombo *et al.*, 1971; Gibson, 1973; Popp *et al.*, 1975; Stefadouros and Canedo, 1977). However, these studies have differed in technique and type of variation studied, and

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consequently it was decided to measure the variability and, therefore, reproducibility of echocardiographic measurements of left ventricular function specifically under the circumstances appropriate to the investigation of drug action.

Subjects and methods

Echocardiography was performed using an Ekoline 20A Ultrasonascope with a 2·25 MHz, 1·3 cm diameter, 10 cm focus transducer in conjunction with an Ekoline 21 Strip Chart Recorder.

Recordings were taken from the standard interspace (Popp *et al.*, 1975) where the mitral valve was seen clearly with the transducer perpendicular to the chest wall. Machine controls were adjusted to show the septal and posterior wall endocardium clearly throughout the cardiac cycle. An M mode scan was then made from the aorta to the apex and the position where the echo from the mitral posterior leaflet was first replaced by chordal echoes was used to define the position where tracings were then recorded with the transducer stationary (Fig. 1). A carotid artery pressure tracing was recorded simultaneously on the echocardiographic tracing using a Hewlett Packard pressure transducer (2105 1D). Only subjects in whom the whole procedure could be carried out unequivocally were used in the study (10 out of 15 normal subjects). Tracings were recorded at 100 mm/s paper speed and measurements were made on 3 out of 6 consecutive beats during quiet respiration (Gerstenblith *et al.*, 1977) and the mean results were taken.

End-diastolic diameter (EDD) was defined as the distance between the septal and posterior wall endocardial echo at the peak of the R wave on the simultaneously recorded electrocardiogram, and end-systolic diameter (ESD) was measured at the point of least perpendicular separation of the endocardial surfaces (Fortuin *et al.*, 1971). Distances were measured using the internally generated scale whose reproducibility was checked with a reference echo (coefficient of variation = 1%) and expressed to the nearest mm. Heart rate was measured as the mean of the 6 consecutive beats recorded on the electrocardiogram.

End-diastolic volume (EDV) in ml and end-systolic volume (ESV) in ml were estimated as the cube of the respective diameters (Pombo *et al.*, 1971). Other indices were estimated from standard derivations: diameter shortening (ΔD) = (EDD − ESD) cm; stroke volume (SV) = (EDV − ESV) ml; ejection fraction (EF) = $\frac{\text{SV}}{\text{EDV}}$; cardiac output (CO) = (SV × HR) ml; percentage diameter shortening (%ΔD) = $\frac{\text{EDD} - \text{ESD}}{\text{EDD}} \times 100$) per cent.

The mean normalised rate of circumferential fibre shortening, which has been suggested as a possible measure of contractility (Cooper *et al.*, 1972), was calculated as $\left(\frac{\text{EDD} - \text{ESD}}{\text{EDD} \times \text{ET}}\right)$ circumferences/s

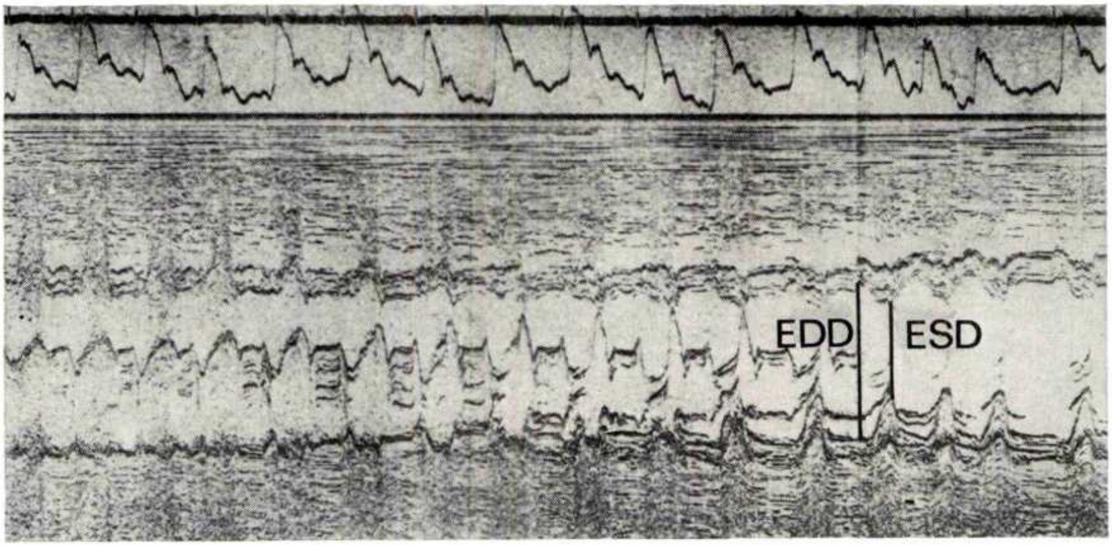

Fig. 1 *M mode scan to define ventricular level for diameter measurements.*

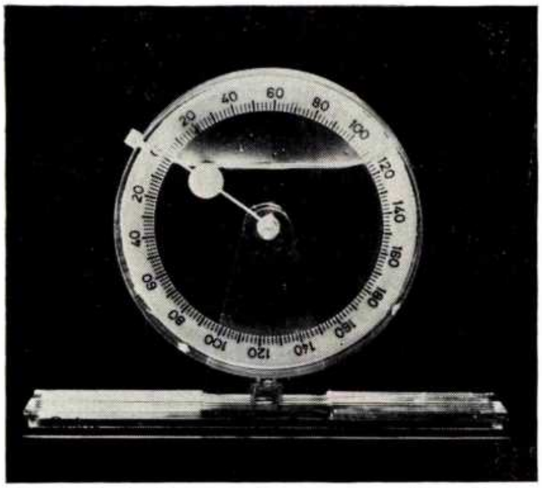

Fig. 2 *Device for measuring the degree of the subject's lateral rotation.*

where ET = ejection time in seconds. Ejection time was measured as the time interval from the upstroke to the dicrotic notch of the simultaneous carotid artery tracing using the internal time scale. The accuracy of this scale was confirmed by a standard time pulse (coefficient of variation = 2%) and the mean of the 3 beats used in the diameter measurements was taken. A previous comparison of ejection time measured in this way with that measured directly from aortic valve echoes showed close correlation ($r = 0{\cdot}98$, $P < 0{\cdot}001$, $n = 9$).

The initial tracings were evaluated using the wall volume method for reliability (Bennett and Rowlands, 1976). Recordings were taken in the subject position where clear tracings could be obtained. The degree of each subject's cranial elevation was defined by the angle from the horizontal made by the adjustable back of the examination couch. The degree of lateral rotation, if any, was measured with a simple device designed for measuring the angle of movement at major joints (Fig. 2). This allowed subjects to be included in whom acceptable tracings were not obtained in the supine position, thus increasing the yield of suitable subjects.

On each occasion, the exact subject position was recorded along with the interspace used and the machine control settings. On all subsequent occasions these variables were reproduced, since controlling subject position and interspace had been shown in a preliminary study to reduce significantly the variance of sequential measurements.

In this study 2 diameter measurements were made in 5 subjects using different interspaces with subject position controlled and in different positions with interspace controlled. Two further measurements were then made with both variables controlled. In each case the variance was measured and compared. (Positional variance ratio for diameters $= 7{\cdot}1$ $P < 0{\cdot}01$; interspace variance ratio $= 5{\cdot}7$ $P < 0{\cdot}05$.)

The appropriate ventricular level for recordings was confirmed by matching the echocardiographic pattern from the mitral valve and/or apparatus in the tracings taken on each occasion in each individual (Fig. 3).

Using the above technique, short-term reproducibility was measured in 10 normal subjects

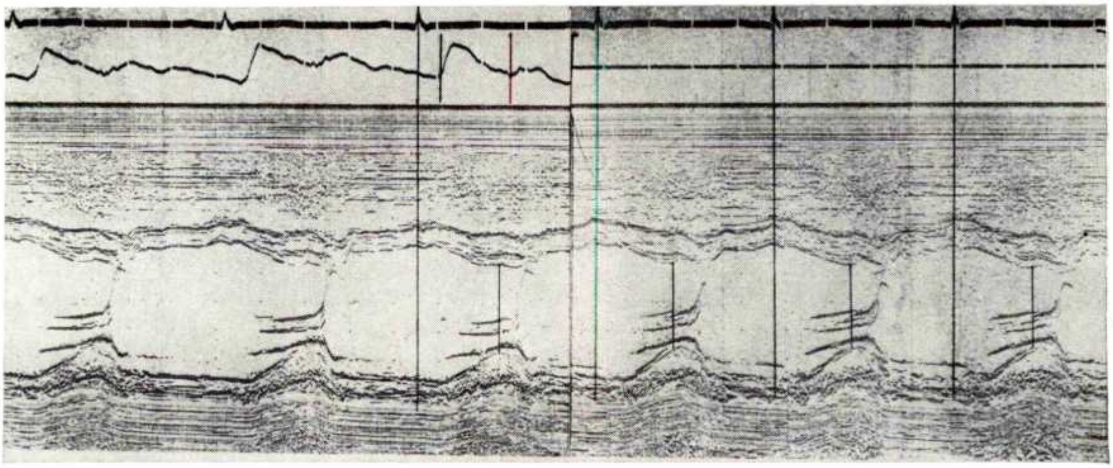

Fig. 3 *Two echocardiograms from a normal subject recorded one week apart.*

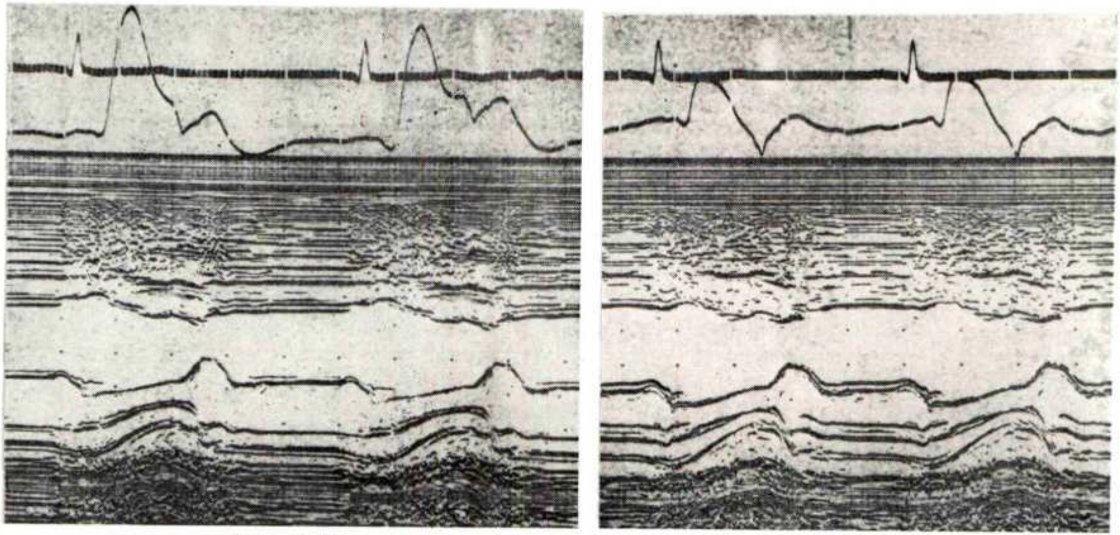

Fig. 4 *Effect of sublingual glyceryl trinitrate on ventricular internal diameters.*

(7 men, 3 women, age 21 to 38). Three measurements were made of the ventricular internal diameters at approximately 5-minute intervals. In between recordings the transducer was removed from the chest and then repositioned while the subjects maintained a constant posture.

The mean, range, standard deviation, and coefficient of variation of the ventricular diameters and all the derived indices were measured for each subject and the group means were calculated.

In a smaller group of these subjects (n = 5) sequential reproducibility was studied in greater detail during the course of drug studies. Each of the 5 subjects was given 0·5 mg glyceryl trinitrate sublingually after 3 control tracings at 5-minute intervals and echocardiographic recordings were made 5 minutes later, along with further measurement of pulse rate and blood pressure. During another study baseline measurements were made at the same time of day on 4 different days, one week apart. On one of these days the subjects received placebo after the baseline recording and measurements were made at hourly intervals for 6 hours.

Statistical analysis of the results was by Student's paired t test and an analysis of variance incorporating replicate control measurements.

The individual measurements from the 3 beats used from each tracing gave an estimate of beat-to-beat variation, and the control measurements of the trinitrate study (n = 3) were used to measure immediate variability. Similarly the placebo day results were used as a measure of hourly variation (n = 7) and the baseline measurements on each study day (n = 4) as a measure of weekly variability. The effect of time interval between tracings on variability was assessed by comparing the first 3 measurements at each time interval. Short-term variability was remeasured after an interval of 1 year from the initial recordings. Short-term variability was also measured in a small group of patients with ischaemic heart disease without significant dyskinesia (n = 5), and hourly variation was measured in a group of hypertensives (n = 5). All the normal subject data were used to estimate the changes in echo diameters and derived indices which would have to occur, after pharmacological intervention, to give a high chance of being shown to be statistically significant.

These estimates were used as a measure of the sensitivity of the method under a variety of different experimental designs. The designs considered differed in the time interval between measurements, the number of tracings taken on each occasion, and the number of subjects examined. The influence of these factors on estimated sensitivity was examined in an attempt to define the optimum application of echocardiography to cardiovascular drug assessment.

Results

The immediate variation measured in the whole normal group was small, showing good short-

Table 1 *Sequential variation in 3 measurements: group mean of individual mean results*
Time interval = 5 min

	Mean			*Range*			*Standard deviation*			*Coefficient of variation* (%)		
	N = 10	*N = 5*	*N = 5*	*N = 10*	*N = 5*	*N = 5*	*N = 10*	*N = 5*	*N = 5*	*N = 10*	*N = 5*	*N = 5*
	T = 0	*T = 0*	*T = +1 y*	*T = 0*	*T = 0*	*T = +1 y*	*T = 0*	*T = 0*	*T = +1 y*	*T = 0*	*T = 0*	*T = +1 y*
EDD (cm)	4·6	4·5	4·4	0·14	0·12	0·11	0·08	0·07	0·06	1·7	1·6	1·3
ESD (cm)	3·1	3·1	3·1	0·11	0·11	0·12	0·06	0·06	0·06	1·9	2·0	2·0
ΔD (cm)	1·5	1·4	1·3	0·11	0·10	0·11	0·06	0·06	0·06	4·0	4·1	4·4
EDV (ml)	94	93	90	10	8	6	5	4	3	5·6	4·9	3·9
ESV (ml)	27	30	30	3	3	3	2	2	2	6·3	6·6	5·5
SV (ml)	67	63	60	8	6	6	4	3	3	6·5	5·7	5·5
CO (l)	4·27	4·12	3·90	0·56	0·53	0·49	0·43	0·28	0·25	7·1	7·2	6·2
EF	0·71	0·68	0·68	0·03	0·03	0·03	0·02	0·01	0·02	2·3	2·0	2·4
%ΔD	34	32	32	2·3	2·2	2·2	1·2	1·2	1·2	3·6	3·6	3·9
VCF (circ/s)	1·14	1·11	1·10	0·10	0·07	0·09	0·05	0·04	0·05	4·6	3·3	4·3

T = Time of measurement.

term reproducibility using the above method. There was no difference between the overall group and the subset of 5 subjects who were studied in detail, suggesting that they were a representative sample (Table 1). In these 5 normal subjects the sequential variation in measurements increased with increasing time interval on almost every occasion (Table 2). Measurement of immediate variability remained unchanged even after a gap of 1 year (Table 1), and the difference in individual mean diameters 1 year apart was in no case greater than 0·3 cm and the changes were random. There was no significant difference in variability in either group of patients compared with the normal subjects for the appropriate time intervals (Table 2).

The estimates of the size of change in each measurement which would have to occur to be statistically significant varied with time interval, number of measurements made, and subject numbers. The size of the change under these different circumstances which would ensure a 95 per cent probability of an observed difference being declared significant at the 5 per cent level is shown in Table 3.

In all subjects both ventricular diameters decreased significantly after glyceryl trinitrate (Fig. 4). Estimated ventricular and stroke volumes decreased but since heart rate increased cardiac output was unchanged. The ejection phase indices (EF, %ΔD, V_{CF}) all increased significantly (Table 4).

Discussion

The size of sequential variation in echo diameters in this study was similar to some previous studies but substantially smaller than other reports. The more pessimistic of the previous estimates mainly come from an earlier phase in the development of the echocardiographic application to left ventricular measurement, where standardisation was not as rigid as now appears optimum. Initially the exact level through the mitral apparatus was not defined in detail (Pombo *et al.*, 1971) and the concept of standard interspace, which has been shown to reduce variability (Popp *et al.*, 1975) was not in use. The use of strip chart recorders rather than Polaroid photographs has improved resolution and the careful control of all variables which we have attempted to maintain during repeated measurements should have allowed us to keep random variability to a minimum.

Previous work has not compared variability at different time intervals. Sequential variation in

Table 2 *Effect of time interval on reproducibility of echocardiographic diameters: group mean of individual mean results in cm*

Interval	*Range*			*Standard deviation*			*Coefficient of variation* (%)		
	EDD	*ESD*	*ΔD*	*EDD*	*ESD*	*ΔD*	*EDD*	*ESD*	*ΔD*
Normals n = 5									
Beat to beat	0·08	0·07	0·10	0·04	0·04	0·05	1·0	1·3	3·8
Five minutes	0·12	0·11	0·10	0·07	0·06	0·06	1·6	2·0	4·1
One hour	0·13	0·20	0·14	0·08	0·08	0·08	1·8	3·3	5·8
One week	0·26	0·17	0·24	0·17	0·10	0·12	3·4	3·3	8·4
Ischaemic heart disease n = 5									
Five minutes	0·14	0·13		0·06	0·07		1·4	1·7	
Hypertension n = 5									
One hour	0·21	0·10		0·10	0·06		2·5	2·1	

Table 3 *Magnitude of minimum change with 95 per cent probability of being true change ($P < 0{\cdot}05$)*

Time interval	*Weeks*	*Weeks*	*Hours*	*Minutes*	*Minutes*	*Minutes*	*Minutes*
No. of recordings							
1st occasion	1	1	1	1	1	3	3
2nd occasion	1	1	1	1	1	3	1
Subject no.	5	10	5	5	10	5	5
EDD (cm)	0·39	0·24	0·23	0·19	0·12	0·09	0·14
ESD (cm)	0·27	0·17	0·34	0·17	0·11	0·09	0·13
ΔD (cm)	0·36	0·22	0·32	0·17	0·11	0·08	0·12
EDV (ml)	22	14	14	11	7	6	8
ESV (ml)	7	4	9	5	3	2	3
SV (ml)	21	13	13	9	6	5	7
CO (l)	1·39	0·91	1·26	0·83	0·52	0·40	0·59
EF	0·08	0·05	0·10	0·04	0·03	0·02	0·03
%ΔD	6·2	3·9	7·3	3·4	2·1	1·7	2·4
VCF (circ/s)	0·22	0·14	0·29	0·12	0·07	0·06	0·08

echocardiographic measurements varies with the different time intervals, and the technique therefore will vary in sensitivity in different types of study.

Measurements every few minutes would be needed in an evaluation of short acting drugs such as glyceryl trinitrate. Variation here should represent measuring error, respiratory variation, and variability associated with transducer replacement. It was found to be small (coefficient of variation in diameter = 2%) and similar to a previous study using a carefully controlled technique (Popp *et al.*, 1975). Hourly measurements would be suitable for many single dose and infusion studies, and weekly or longer time intervals would be necessary for steady state evaluations.

These time intervals would also include variation from subject repositioning. They would also include any true change in heart size secondary to intrinsic changes in the determinants of cardiac performance that might occur. These sources of variation might be expected to differ between subjects.

The size of sequential variation with the longer time intervals (coefficient of variation in diameters—hourly 3·5%, weekly 5%) was significantly smaller than some previous studies (Pombo *et al.*, 1971; Stefadouros and Canedo, 1977) but similar to long-term measurement of control subjects in a transplant study (Popp *et al.*, 1971).

The time interval between measurements used in a drug study will be dictated by the pharmacology and kinetics of the drug concerned. Repeated echocardiographic measurements have been shown to be feasible for all the appropriate time intervals and their reproducibility suggests that the method could be sensitive enough to measure clinically relevant drug-induced changes in heart size. Even after a period of 1 year the group mean of individual mean absolute differences in diameters was no more than 0·2 cm.

For optimal use of echocardiography it is necessary to increase sensitivity wherever possible as some drugs may produce only small changes in heart size. If sequential variability in a measurement is known for a given population, the size of the minimum induced change which can be identified can be estimated. This minimum difference was estimated for all the echocardiographic indices and used as a measure of sensitivity. The

Table 4 *Effect of 0·5 mg glyceryl trinitrate sublingually ($N = 5$)*

Control measurements × 3	*Group mean ± 1 standard deviation (1 SD)*	*5 min after glyceryl trinitrate Mean ± 1 SD*	*Significance*
EDD (cm)	4·5 ± 0·53	4·1 ± 0·70	***
ESD (cm)	3·1 ± 0·40	2·8 ± 0·60	***
ΔD (cm)	1·4 ± 0·16	1·3 ± 0·20	
EDV (ml)	93 ± 29	75 ± 29	***
ESV (ml)	30 ± 10	23 ± 10	***
SV (ml)	63 ± 19	53 ± 20	***
HR (beats/min)	67 ± 8	80 ± 3	***
CO (l/min)	4·12 ± 1·0	3·96 ± 1·50	
EF	0·68 ± 0·03	0·72 ± 0·05	**
%ΔD	32 ± 2	34 ± 5	*
ET (s)	0·284 ± 0·02	0·258 ± 0·02	***
VCF (circ/s)	1·11 ± 0·10	1·34 ± 0·30	***
S (mmHg)	117 ± 4	104 ± 6	***
D	76 ± 3	69 ± 6	**

*$P < 0{\cdot}05$ **$P < 0{\cdot}01$ ***$P < 0{\cdot}001$

S, systolic blood pressure; D, diastolic blood pressure.

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minimum differences shown are all small in absolute terms (for diameters 0·1 to 0·4 cm). However, under conditions of minimum sensitivity some indices would have to change by more than one-third to be significant and there is up to a fourfold difference between the estimated minimum and maximum sensitivity.

The estimated sensitivity of the method increased not only when the number of subjects was increased but also when more than one recording was made at intervals of a few minutes on each occasion. In the latter case the increase in sensitivity arises because the variation in the repeated recordings made on each occasion can be used to assess experimental error, thus separating the components of variation attributable to subject repositioning and any associated random changes which differ between subjects. The sensitivity of this design remains constant at different time intervals. The form of statistical analysis used in this situation is to analyse the data as arising from a two-way classification model with an interaction term and replicate observations in each cell. It can be shown that a similar increase in sensitivity may be obtained either by doubling the subject numbers or by making replicate recordings on each occasion (Table 3). This may be important logistically as it is usually far easier in studies to perform multiple measurements on each subject on each occasion than to use more subjects.

These estimates, however, make a number of assumptions. It is assumed that this study group, though small, was representative. This appears valid compared with the whole group of 10. However, it is possible that there might be differences in subjects with cardiovascular disease. Though this is not certain for all types of cardiac disease, variability in repeated hourly measurements in hypertensives and of 5-minute measurements in patients with coronary artery disease without dyskinesia was the same as the normal group. The estimates also presume that all subjects would react to interventions similarly both qualitatively and quantitatively and therefore probably represent idealised estimates. These estimates should, therefore, not be considered highly accurate in themselves. However, they should accurately reflect the way that changing subject numbers or measurement frequency will affect sensitivity.

If relatively large consistent changes occur in echocardiographic indices in a drug study, such as those shown with glyceryl trinitrate (Table 4), some will appear significant with single echocardiographic measurements in a small group. However, in circumstances where the changes are small or variable the increased sensitivity of multiple measurements and more efficient statistical analysis may be necessary to demonstrate significance. For example, when the trinitrate data were assessed by a Student's paired t test using only one control measurement the changes in some indices (EF, $\%\Delta D$, V_{CF}) were not shown to be significant. This was also true when, as is common practice, the 3 control measurements were used only to calculate mean control results. In both cases the other indices were shown to be significant but at a lower level of significance. However, by employing an analysis of variance which took into account the multiple measurements, individual variability could be determined, allowing a more sensitive statistical assessment (Table 4).

When the effects of glyceryl trinitrate were assessed in this study all the derived echocardiographic haemodynamic indices were estimated. The accuracy of these derived indices is limited by the assumptions involved in using the cube formula and may have variable validity in different subjects. They appear to be reasonably sound when applied to normal sized hearts (Fortuin *et al.*, 1971) but can produce substantial errors in subjects with cardiac disease (Popp *et al.*, 1973) especially where dyskinesia is present (Teichholz *et al.*, 1976). However, alternative methods of estimation such as using regression equations (Fortuin *et al.*, 1971) or correction formulae (Teichholz *et al.*, 1976) have not been shown to produce greater accuracy on general application (Cooper *et al.*, 1972; Martin, 1978). In consequence some workers have suggested avoiding derivations (Fortuin and Pawsey, 1977). However, if the cube formula is applied to subjects without dyskinesia before and after drug interventions then it is likely that whatever errors are present will remain reasonably constant throughout, allowing valid measurement of any drug-induced changes.

The changes in estimated haemodynamics after glyceryl trinitrate in this study group are compatible with the effects of a reduction in preload and afterload with compensatory adjustments. These changes are similar to those seen in angiographic studies (McAnulty *et al.*, 1975) and suggest that derived echocardiographic data can give insight into the haemodynamic effects of the drug's action, as has previously been suggested (Burggraf and Parker, 1974).

Echocardiography therefore appears to be a useful method of assessing the effects of cardiovascular drugs on the heart where there is no dyskinesia and when using individuals as their own controls. If the method is standardised rigidly it appears to have good reproducibility. In studies with rapidly changing drug effects it is recommended that a number of baseline measurements be taken every few minutes followed by single subsequent measurements. In single dose studies it would be prudent to take a number of baseline measurements on each day for comparison as well as including a placebo day, modifying the statistical analysis accordingly to take full advantage of the replication of measurements. Similarly in steady state evaluations multiple measurements will allow optimum application of this potentially useful non-invasive method of cardiovascular drug assessment.

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Nomenclature and classification of congenital heart disease

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SUMMARY At present there is no universally accepted nomenclature for congenital cardiac malformations. Much of the controversy results from failure to distinguish the structural connections of the heart from the morphology and spatial relations of its components. The confusion is compounded by an abundance of individual definitions, many of them speculative.

The present article proposes a totally descriptive nomenclature. It describes in turn the connections of the cardiac segments, their morphology, their relations, and additional anomalies in any segment. Each step in the segmental approach is discrete. The overall effect is to force a succinct and comprehensive description of any cardiac malformation, no matter how complex.

To be of value, a nomenclature must allow all congenital heart defects to be described unambiguously, accurately, and succinctly. It must assist the clinical cardiologist to diagnose and describe all these anomalies during life. It must be compatible with the morphological findings so that it is as valid for examinations at operation or necropsy as it is during diagnostic investigations. A classification and nomenclature should not be difficult to learn or to remember. Clarity, not erudition, is the touchstone of success.

It is our contention that classifications at present in use do not satisfy these criteria. They lack flexibility and are frequently derived from morphogenetic concepts which are more or less speculative. In the less flexible systems, where a Procrustean approach is necessary, attempts to make them comprehensive result in sub-classifications with alphabetical and numerical designations (Edwards and Burchell, 1949) which have no descriptive value. In those based in part upon deductions from normal embryology, changes in nomenclature are frequent and depend upon the authority whose theories are considered to be most valid at that time or in that place (de la Cruz and Nadal-Ginard, 1972; Van Praagh, 1972).

There is little doubt that a segmental approach (Van Praagh *et al.*, 1964; de la Cruz and Nadal-Ginard, 1972; Van Praagh, 1972; Kirklin *et al.*, 1973; de la Cruz *et al.*, 1976) to description is logical, but there is no consensus on how to employ this analytical method (Shinebourne *et al.*, 1976; Brandt and Calder, 1977). For example, a recent article (Stanger *et al.*, 1977) was accompanied by an editorial and glossary (Van Praagh, 1977) to facilitate its comprehension. Since the glossary contained such cryptic terms as 'isolated atrial non-inversion' and 'isolated ventricular discordance' its success was limited!

In any segmental approach, the prime requirement is the identification of the components of each cardiac segment. Then, since the route of the circulation is fundamental to the physiology and treatment of congenital heart disease, nomenclature should be based on the connections of the segments. Consideration of the connections must not exclude attention to and description of the relations of the segments nor obscure awareness that variations in chamber morphology can exist with the same connections.

The most productive way of using the sequential approach is to employ a synthesis of connections,

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Table 1

(A) Define atrial situs
(B) Describe atrioventricular junction
    (i) Connections
    (ii) Mode of connection
    (iii) Ventricular morphology (if not specified by (i))
    (iv) Relation of chambers in ventricular mass
(C) Describe ventriculoarterial junction
    (i) Connections
    (ii) Relation of arterial valves and great arteries
    (iii) Morphology of outflow tracts
(D) Define additional anomalies

morphology, and relations at each junction of the cardiac segments. Thus connections, morphology, and relations must be described both at the junction of the atria with the ventricles and between the chambers in the ventricular mass and the great arteries.

The segmental approach proposed by some of us (Shinebourne *et al.*, 1976) has proved to have deficiencies and does not provide this synthesis. It has been modified to provide a comprehensive and easily assimilable nomenclature.

(A) **Steps employed in descriptive analysis (Table 1)**

The initial step is to identify the atrial situs. The analysis of the atrioventricular junction is then performed. The type and mode of atrioventricular connection are determined. In most instances, this process will include identification of ventricular morphology. If not identified, this must be established. Then the relations of chambers in the ventricular mass are described. This same process is then repeated at the level of the junction of the great arteries with the ventricular mass, identifying connections, relations, and the morphology of the outflow tracts. Finally, knowing the route of circulation and the anatomy and relations of the cardiac chambers, additional cardiac anomalies are described.

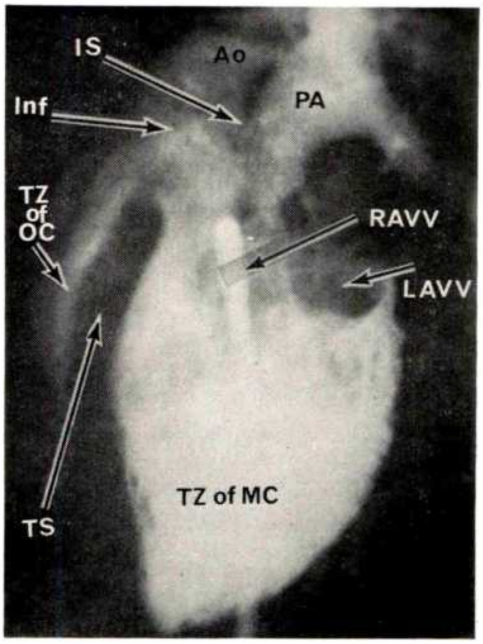
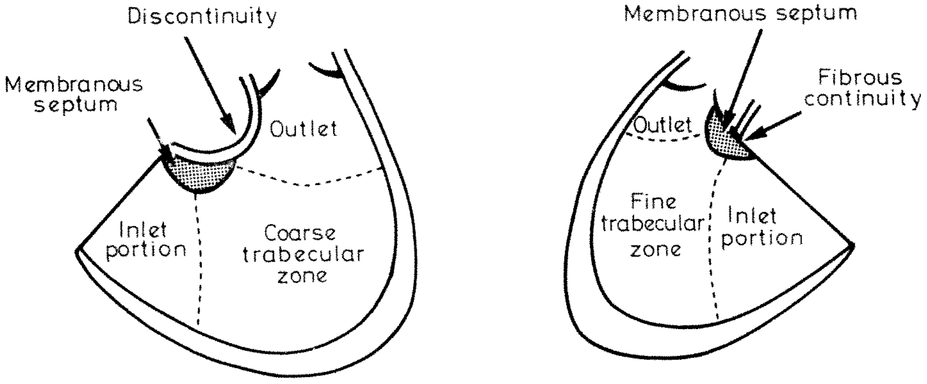


Fig. 1 *Angiogram taken so as to show the septum between the chambers in profile in an example of 'single ventricle with outlet chamber' (univentricular heart of left ventricular type). The anterior chamber has both an outlet component (OC) and a trabecular component. It is not merely an infundibular chamber, but is a rudimentary chamber of right ventricular type separated from the main chamber (MC) by the trabecular septum (TS). Ao = aorta; PA = pulmonary artery; Inf = infundibulum; TZ = trabecular zone; IS = infundibular septum; RAVV, LAVV = right, left atrioventricular valve. See also Fig. 8. Angiogram provided by courtesy of Dr B. Soto, University of Alabama in Birmingham, Birmingham, Alabama, USA.*

(B) **Definitions**

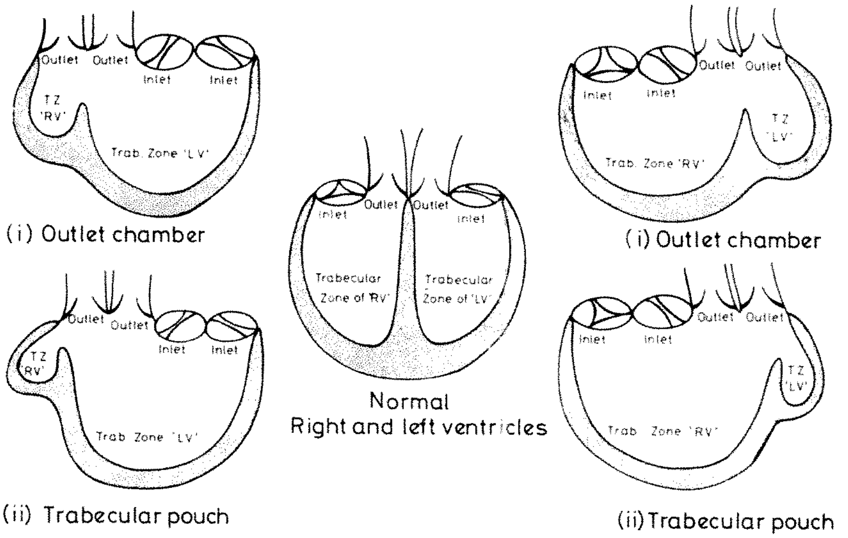
There is little controversy concerning definition and terminology of atrial chambers (Van Praagh *et al.*, 1964; de la Cruz *et al.*, 1976; Shinebourne *et al.*, 1976). However, less agreement exists with regard to the nomenclature and anatomy of chambers within the ventricular mass (Lev, 1954; Van Praagh *et al.*, 1964; Lev *et al.*, 1969; de la Cruz *et al.*, 1976; Shinebourne *et al.*, 1976). For example, the term 'single ventricle' is used to describe hearts which possess 2 chambers within their ventricular mass (Van Praagh *et al.*, 1964; Lev *et al.*, 1969). It is implicit in this usage that one of these chambers is not a ventricle. This is a problem which cannot be ignored, nor dismissed on the basis that one chamber is merely the infundibular or conus portion of the right ventricle (Van Praagh *et al.*, 1964). Such chambers contain, in addition to an infundibulum, a discrete trabecular zone separated from the main chamber by a trabecular septum (Fig. 1). To clarify this situation, it is necessary to define the minimal requirements for a chamber to be considered a ventricle. The initial step in this process is to be clear concerning the components of a *normal* ventricle. Goor and Lillehei (1975) have suggested that normal ventricles possess 3 components, and our observations endorse this opinion. In descriptive terms these components are the inlet component, the trabecular component, and the outlet or



(a) Normal right ventricle (b) Normal left ventricle

Fig. 2 *Diagrammatic representation of the components of normal ventricles. In such normal ventricles, the transition between the components is indistinct.*

infundibular component (Fig. 2). The *ventricular inlet component* comprises the portion downstream of an atrioventricular valve annulus whether that valve be patent or imperforate. The anatomical presence of an inlet component is unrelated to the patency of its valve. The *ventricular trabecular component* comprises the body of the ventricle distal to the insertion of the papillary muscles. The trabecular pattern is distinctive and is independent of both inlet and outlet. Thus a distinction can be made between a trabecular portion of morphologically right ventricular type and one of morphologi-



(i) Outlet chamber (i) Outlet chamber

Normal Right and left ventricles

(ii) Trabecular pouch (ii) Trabecular pouch

A Rudimentary chambers of RV type in univentricular heart LV type

B Rudimentary chambers of LV type in univentricular heart RV type

Fig. 3 *Diagrammatic representation of the possible types of rudimentary chamber compared with normal right and left ventricles. Rudimentary chambers of right ventricular (RV) type coexist with main chambers of left ventricular (LV) type giving univentricular hearts of left ventricular type. Rudimentary chambers of left ventricular type are found in univentricular hearts of right ventricular type, the main chamber having the trabecular zone of the right ventricle. Rudimentary chambers can exist with double outlet, but are not illustrated.*

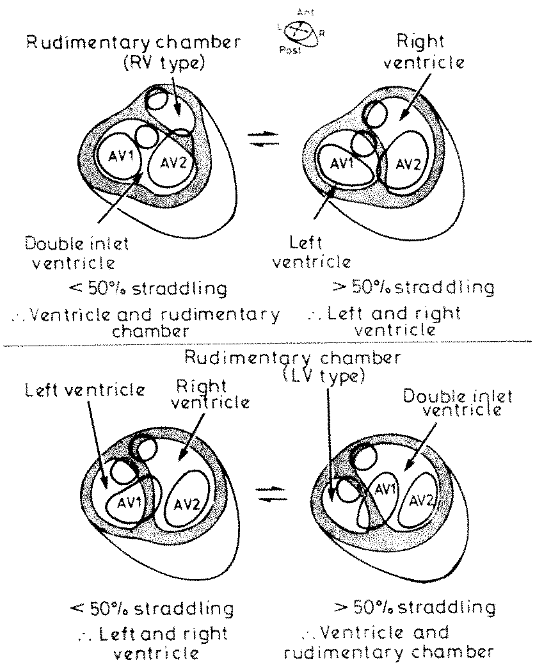


Fig. 4 *Diagram illustrating the spectrum which exists when the right (upper diagrams) or left (lower diagrams) atrioventricular valve straddles the ventricular septum. The degree of straddle refers to the amount by which the valve is committed to the chamber with right ventricular characteristics. It is suggested that 50 per cent straddling be the 'cut-off' point for assigning an atrioventricular valve to a chamber in the ventricular mass. These illustrations do not depict every situation in which straddling occurs, but wherever a valve straddles a septum the principles remain the same.*

cally left ventricular type. The *ventricular outlet component* supports the arterial valve of the ventricle. It may be a complete muscular structure, or may be attentuated to permit continuity between the atrioventricular and arterial valves.

A *normal ventricle* has all 3 components. However, the left ventricle in double outlet right ventricle is generally accepted to be a ventricle though it has no outlet component. In accordance with common usage, therefore, the outlet component is not essential for a chamber to be considered a ventricle. We suggest that the minimal requirements for a chamber to be considered a ventricle are that it possesses an inlet portion and a trabecular portion as defined above. Chambers which do not possess an inlet portion are not ventricles and are described as *rudimentary chambers*. They may be of left or right ventricular type depending upon the nature of their trabecular portion (Fig. 3). They may be of two varieties—*outlet chambers* which possess both trabecular and outlet portions or *trabecular pouches* having only a trabecular part (Fig. 3). Each of these varieties may be of left or right ventricular type.

In the normal heart, the inlet and outlet portions of each ventricle are unequivocally committed to their respective trabecular zones. However, in malformed hearts it is known that either or both inlet and outlet components can straddle or override the septum separating the trabecular portions (Liberthson *et al.*, 1971; Quero Jiménez *et al.*, 1973). Between the situations in which inlet or outlet components are entirely committed to one ventricle or the other, there is a continuum of variation that cannot be glossed over. Any classification must cater for this contingency. In the case of overriding arterial valves, Kirklin *et al.* (1973) suggested that they be assigned to the ventricle supporting more than half the valve circumference. We suggest that this concept be extended to straddling or overriding inlet components and that such components also be assigned to the chamber connecting to more than half their atrioventricular annulus. A chamber in the ventricular mass is judged to possess an inlet component, and hence be a ventricle, when its connection is to more than half an atrioventricular valve annulus (Fig. 4). When this condition is not fulfilled, it is a rudimentary chamber. A rudimentary chamber is defined as an outlet chamber when it supports more than half an arterial valve annulus. It is a trabecular pouch when the trabecular portion in question is connected to less than half the circumference of both an atrioventricular and an arterial valve (Fig. 5).

In the presence of a common atrioventricular valve connecting both atria to both chambers in the ventricular mass, where this can, by inspection of the attachment of valve leaflets to the ventricular mass, be divided into mitral and tricuspid components, these should be treated as described for separate mitral and tricuspid valves. Where the common valve cannot be so divided both these chambers are defined as ventricles if they each receive more than 25 per cent of the orifice of the common valve. If one receives less than 25 per cent it is considered not to have an inlet portion and therefore to be a rudimentary chamber.

This approach to straddling or overriding valves aims at providing a means of making decisions when the atrioventricular or arterial connections are in doubt. Since such decisions involve arbitrary subdivisions of a continuous spectrum of anomalies, and are made using methods where precise quantification is difficult, the estimated degree of overriding or straddling should be included in the description of the heart.

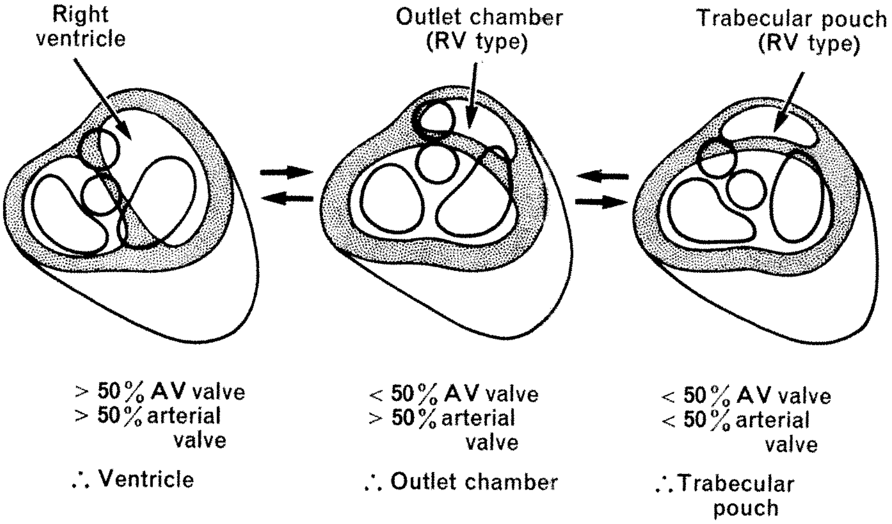


Fig. 5 *Diagram illustrating the spectrum from a ventricle through an outlet chamber to a trabeculated pouch. The spectrum illustrated is of rudimentary chamber of right ventricular type. A similar spectrum exists for rudimentary chambers of left ventricular type. For simplicity, the question of concordance or discordance and the possibilities of double outlet rudimentary chamber or single outlet heart have been omitted.*

(C) Determination of atrial situs

There are 3 varieties of atrial situs. These are situs solitus, situs inversus, and situs ambiguus (Van Mierop *et al.*, 1970). In the presence of situs solitus or inversus of the viscera, it is exceedingly rare for atrial situs not to reflect this visceral situs. Therefore, atrial situs can usually be established from visceral situs. In doubtful situations, particularly in the presence of situs ambiguus, bronchial anatomy is more reliable than the situs of the abdominal viscera as a guide to atrial situs. Partridge *et al.* (1975) showed that bronchial situs could be reliably identified radiologically because the morphologically left main bronchus is significantly longer than the morphologically right main bronchus. If both bronchi are approximately the same length, then bronchial isomerism exists and situs ambiguus of the atria is likely. Though bronchial anatomy is the best clinical guide to atrial situs, it is known that in rare cases atrial morphology does not correspond with bronchial anatomy (Brandt and Calder, 1977; Macartney *et al.*, 1978). Where such a situation is

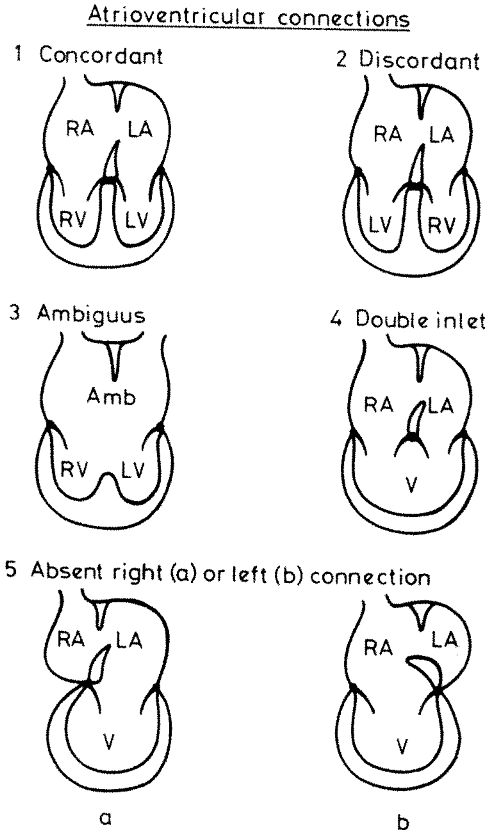


Fig. 6 *Diagrammatic representation of the possible types of atrioventricular connection. Where lateralisation is present, the diagrams illustrate situs solitus. The same possibilities exist and the same terms are used for situs inversus.*
Abbreviations: RA, right atrium; LA, left atrium; Amb, ambiguus atria; RV, right ventricle; LV, left ventricle; V, ventricle in the ventricular mass.

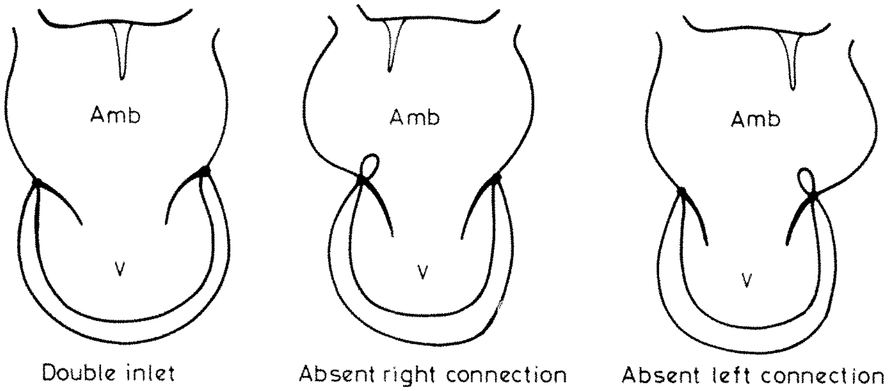


Fig. 7 *Diagram illustrating how double inlet or absence of right or left atrioventricular connection can exist with ambiguus atria.*

suspected, the question can only be resolved by demonstration of atrial morphology, either by angiocardiographically injecting contrast medium into the atrial appendages or by direct inspection.

(D) Description of atrioventricular junction

(i) ATRIOVENTRICULAR CONNECTIONS

There is little problem in defining atrioventricular connections when 2 atria connect with 2 ventricles. In these circumstances the possible types of connection are atrioventricular concordance, atrioventricular discordance, or ambiguous atrioventricular connection (Fig. 6). A concordant connection exists when the morphologically right atrium connects to the morphologically right ventricle and the morphologically left atrium to the morphologically left ventricle (Fig. 6.1). Discordance describes the converse connections (Fig. 6.2). In situs ambiguus, when the atria cannot be differentiated one from the other, the connection with 2 ventricles is necessarily ambiguous (Fig. 6.3).

Potential for confusion in defining atrioventricular connections exists when both atria do not connect directly with separate chambers in the ventricular mass, for instance when both atria connect to the same chamber or alternatively when one atrium is not directly connected to any chamber by either a perforate or an imperforate atrioventricular valve. These examples are separate and distinct connections, namely double inlet ventricle (Fig. 6.4) and absence of one atrioventricular connection (Fig. 6.5). Both can exist with solitus, inversus, or ambiguous atrial chambers (Fig. 7). These two connections make up the category of the univentricular heart.

(ii) MODE OF CONNECTION

The mode of atrioventricular connection describes the anatomy of the valve annuli at the atrioventricular junction. In the presence of definitive right and left ventricles without straddling of either atrioventricular valve, then the valves can be described as 'triscupid', 'mitral', or common. In the univentricular heart, it may be impossible even at necropsy to identify definite 'mitral' or 'tricuspid' valve morphology. The non-specific terms 'right' and 'left' atrioventricular valve according to position (Anderson *et al.*, 1977) are therefore preferred in order to minimise confusion. When 2 atria are found to connect with the ventricular mass, the mode of connection may be via 2 perforate valves, one of which may straddle, a common atrioventricular valve which may straddle, or by one perforate and one imperforate valve. In order to diagnose an imperforate valve, rudiments of that valve must be unequivocally demonstrated. Though these rudiments are most frequently identified at necropsy, they can be shown in life angiographically (Macartney *et al.*, 1976) or echocardiographically (Mortera *et al.*, 1977). When rudiments of an imperforate valve are not seen, the terms absent right or left atrioventricular connection are used. In this context these terms characterise both type and mode of connection (Fig. 6.5). However, with an absent connection, the valve present can still straddle, in which case this must be specified together with the degree of straddling.

(iii) VENTRICULAR MORPHOLOGY

When both right and left ventricles are unequivocally present, there is little difficulty in differentiating one from the other. However, when rudimentary chambers are present, as in the univentricular heart, guidelines are needed for their identification as right or left ventricular type. The 2 features that are of value in this respect are the characteristics of the trabecular zones of the chambers and the orientation of the septum within the ventricular mass. The quality of morphological rightness or leftness of a chamber is conferred upon it by the structure of the trabecular zone and is independent of its connections. Thus a chamber, be it a ventricle or rudimentary, is of right ventricular type when its trabeculations, particularly those on the septum, are coarse while a chamber of left ventricular type has finer trabeculations and a smooth septal surface. Unlike the septum separating 2 ventricles, that separating a rudimentary chamber from a main chamber may not necessarily be directed to the crux of the heart. In the case of rudimentary chambers of right ventricular type, the septum is anteriorly placed and is orientated towards the acute margin of the heart. In contrast, when a rudimentary chamber of left ventricular type is present, the septum is orientated posteriorly to the crux of the heart.

The description of a rudimentary chamber as being of right or left ventricular type implies that the trabecular zone of the main chamber is of the converse type. Thus the description of double inlet ventricle with rudimentary chamber of right ventricular type automatically implies that the trabecular zone of the main chamber is of left ventricular type. This is important when considering the diagnosis in life since a ventriculogram of sufficient quality for morphological definition may be more easily obtained when injecting into a small volume rudimentary chamber than into a large volume ventricle. Ventricular morphology in the univentricular heart may be indeterminate when only one chamber is present in the ventricular mass. It may be exceedingly difficult to distinguish this type of morphology from that of a right ventricular univentricular heart with a tiny rudimentary chamber of left ventricular type. However, success in making the distinction is more likely when the observer is aware of the possibilities.

(iv) RELATION OF VENTRICULAR CHAMBERS

Having determined the morphology of chambers in the ventricular mass, it is then necessary to identify their relations. Right ventricles are described relative to left ventricles, and may be to right or left, anterior or posterior, and superior or inferior. Rudimentary chambers are described in similar terms relative to the main chamber of a univentricular heart.

Table 2 *Connections of the chambers and great arteries*

Atrioventricular connections
(i) Concordant
(ii) Discordant
(iii) Ambiguous
(iv) Double inlet
(v) Absence of one atrioventricular connection

Arterial connections
(i) Concordant
(ii) Discordant
(iii) Double outlet ventricle or outlet chamber
(iv) Single outlet heart

(E) Description of arterial junction with ventricular mass

There have been problems with the description of the ventriculoarterial junction because the connections of the arteries to the chambers in the ventricular mass have been confused with the relations of the great arteries one to another and with the morphology of the outflow tracts. All 3 attributes are necessary for full categorisation of the junction.

(i) ARTERIAL CONNECTIONS

There are 4 varieties of arterial connection (Table 2). Concordant connections exist when the aorta arises from the morphologically left ventricle or an outlet chamber of left ventricular type and the pulmonary artery from the morphologically right ventricle or an outlet chamber of right ventricular type. Discordant connections exist when the converse is true. Double outlet ventricle or double outlet chamber exist when more than half of both the aorta and the pulmonary artery arise from that chamber. Finally, single outlet heart is present when only one great artery is connected to the ventricular mass. There are 3 types: firstly, single outlet heart via the aorta when the pulmonary artery is not directly connected by a perforate or imperforate valve to the chambers in the ventricular mass; secondly, single outlet heart via the pulmonary artery when the aorta is not directly connected by a perforate or imperforate valve to the chambers in the ventricular mass; and, finally, single outlet heart via a persistent truncus arteriosus when a persistent truncus is connected to the chambers in the ventricular mass. The single great artery may arise from a ventricle or an outlet chamber. In all 3 varieties of single outlet heart the artery is assinged to the chamber which supports more than half its arterial valve.

Because potential connections of atria or great arteries to the ventricular mass are difficult to discern in life, absence of right or left atrioventricular connections and single outlet heart are the designations most likely to be changed by necropsy examination.

(ii) ARTERIAL RELATIONS
When describing the relations of the great arteries, the position of the arterial valves is described one relative to the other in both anteroposterior and lateral planes.

(iii) MORPHOLOGY OF OUTFLOW TRACTS
The morphology of the outflow tracts is independent of both connections and relations. Either or both arterial valves may have a complete infundibulum or may be in fibrous continuity with an atrioventricular valve. It is entirely logical that the situation of double outlet right ventricle may coexist with the morphological entity of tetralogy of Fallot.

(F) Additional cardiovascular abnormalities

These are catalogued in as much detail as the investigations permit and include anomalies of venous return, either pulmonary or systemic, septal defects, and ventricular outlet obstructions. In the majority of cases these 'additional' abnormalities will in fact be the only ones present. Thus, except in those cases with abnormal connections of the cardiac segments, there is little change in the terminology of most congenital cardiac malformations.

Comment

In the introduction we stated why a revision of the classification of congenital cardiac malformations was necessary. In the body of the paper we have presented our solutions to these problems. They differ in several ways from previous classifications. The present nomenclature describes connections, relations, and morphology as interdependent features, all being necessary for full description of the heart. Other approaches have used relations to predict connections (de la Cruz *et al.*, 1976) or else have used relations as interchangeable with connections, as for example in the term 'normally related great arteries' (Van Praagh, 1977).

Just as connections cannot be described in terms of relations, the anatomy of the atrioventricular junction cannot be described by merely indicating the presumed direction of looping of the embryonic heart tube (Van Praagh, 1972). Instead, it is necessary to describe this region in detail. We have chosen to use 4 steps, firstly the overall route of connection (type of connection), secondly the anatomy of the valves at the atrioventricular junction (mode of connection), thirdly the morphology of the ventricular mass, and finally the relation of chambers within it. Kirklin *et al.* (1973) have previously used the terms 'concordant' and 'discordant' introduced by Van Praagh *et al.* (1964) to describe connections at both atrioventricular and ventriculoarterial levels, and we have followed this precedent. However, at the atrioventricular level connections exist which cannot be described accurately using either this terminology or the loop convention. We have used the terms ambiguous connection, double inlet ventricle, and absence of one atrioventricular connection to describe these situations. Using our terminology, together with separate description of chambers within the ventricular mass of the heart, it has proved possible to provide a description of complex anomalies such as the univentricular heart in all its variations, based solely upon the anatomy as it is observed. Using only anatomical features, we have distinguished chambers within the ventricular mass of univentricular hearts as ventricles and rudimentary chambers. This is necessary because 'single ventricle' and 'common ventricle' are in common usage to describe hearts which possess 2 chambers within their ventricular mass (Van Praagh *et al.*, 1964; Lev *et al.*, 1969; Stanger *et al.*, 1977).

The strict distinction between ventricles and rudimentary chambers also permits rationalisation of the problem of hearts with absence of one atrioventricular connection (Anderson *et al.*, 1977). Such hearts, for example in the majority of cases of tricuspid atresia, are at present excluded from the category of the univentricular heart on arbitrary grounds (Van Praagh *et al.*, 1964). Yet comparison of the anterior chambers in hearts with 'single ventricle' and in hearts with 'tricuspid atresia' shows that from an anatomical and descriptive standpoint they are the same (Fig. 8). Our definitions are aimed at eliminating this paradox, yet accentuating the differences within the univentricular group, namely variations in atrioventricular connection and ventricular morphology. Description of both these features are necessary to categorise fully these hearts.

Our proposed descriptive nomenclature takes the classification of congenital heart disease out of the arena of morphogenetic interpretation, since a nomenclature and classification cannot be part of this process and still fulfil the functions outlined in the introduction.

It is abnormal connections and associated abnormalities which may require surgical treatment. An abnormal relation or morphology alone does not need correction. The importance of the relations and morphology of the cardiac segments is in the planning and execution of surgical treatment. We have purposely avoided the use of terms such as

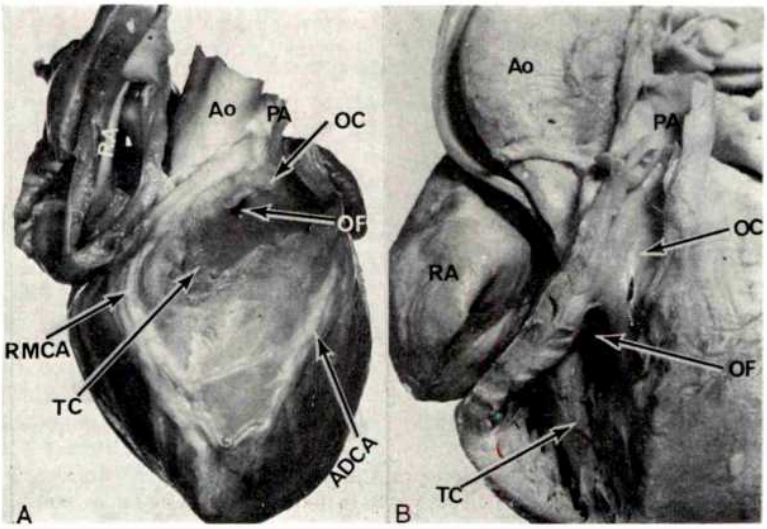


Fig. 8 *Photographs of the anterior chambers in two hearts with arterial concordance and 'normally related' great arteries. Fig. 8A shows a heart with typical 'tricuspid atresia'. The right atrial appendage has been removed, showing the absence of the right atrioventricular connection. The right atrium (RA) is not related to the anterior chamber, which has outlet (OC) and trabecular (TC) components. The anterior chamber communicates with the atrial inlet only via the outlet foramen (OF) and the main chamber. Note that the chamber position is delimited by the marginal branch of the right coronary artery (RMCA) and the anterior descending branch (ADCA) of the left. Fig. 8B shows a heart with double inlet ventricle. The anterior chamber is virtually identical in morphology to the chamber illustrated in Fig. 8A. Both are rudimentary chambers of right ventricular type. (Note coarse trabeculations of trabecular zone in Fig. 8B; Ao, aorta; PA, pulmonary artery.)*

'transposition', 'malposition', 'tricuspid atresia', 'mitral atresia', etc. because they mean different things to different people. We do not suggest that the terms be discarded. Providing that the basic scheme of connections, relations, and morphology is used then confusion cannot ensue.

We thank the members of the Study Group on Congenital Heart Disease in England and Wales, Dr L. H. S. Van Mierop of Gainesville, USA, Dr T. G. Losekoot of Amsterdam, The Netherlands, and our other colleagues and friends in Europe and America who helped during the formulation of the nomenclature. We are particularly grateful to Dr Benigno Soto for permitting us to use one of his profiled angiograms to illustrate a point.

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Prevalence of congenital heart disease in black schoolchildren of Soweto, Johannesburg[1]

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SUMMARY A survey conducted by cardiologists in Soweto, Johannesburg, provided an opportunity of assessing the frequency of congenital heart disease in black schoolchildren. Among 12 050 schoolchildren aged 2 to 18 years, 48 had a congenital heart defect, yielding a prevalence of 3·9 per 1000. Only in 2- to 6-year-old children did the prevalence exceed that of rheumatic heart disease. The distribution of the types of defects was largely similar to that reported in other surveys with a predominance (52%) of ventricular septal defects. Two unusual findings were the unexplained absence of persistent ductus arteriosus in these children, and the detection of 5 children with situs inversus (1 in 2410). In all but one child, the congenital heart defect was first discovered during the survey. Despite the limitations of a prevalence study, it can be concluded that congenital heart disease is at least as common in this South African black community as in Caucasians.

The reported frequency of congenital heart disease in children is influenced by the standards of health care and availability of cardiac services to detect and treat such children. In Africa, where many infants are delivered at home and a large proportion of the population is served by unsophisticated rural health clinics, congenital heart disease has been said to be less common in black children than in white (Schwartz *et al.*, 1958; Shaper and Williams, 1960). Several clinical and necropsy studies (Watler, 1960; Schrire, 1963, 1964; Van der Horst, 1965; Caddell and Connor, 1966; Caddell and Morton, 1967; Van der Horst *et al.*, 1968) have suggested, however, that there is no difference in incidence among the 2 groups, but these studies included only those patients who came to the attention of physicians or cardiologists. In populations in which the seeking of modern medical care is not yet generally accepted, it is probable that many children either die before the heart defect is detected or remain undiagnosed. Estimation of the prevalence of congenital heart disease in black schoolchildren provides some indication of the extent of the problem in a community and also of the frequency with which it is missed through childhood years. It does not reflect the true frequency of congenital heart disease as it does not take into account the large number of children who have died in infancy or early childhood (Campbell, 1973). The high case fatality rate during the neonatal period reduces the incidence from about 8 per 1000 (Landtman, 1965; Kerrebijn, 1966; Carlgren, 1969; Mitchell *et al.*, 1971) at birth to a prevalence of 5 per 1000 at the end of the first year of life (Campbell, 1973) and others will die before reaching school age. Furthermore, many small ventricular septal defects may close spontaneously during the first few years and will not be detected in school surveys (Mitchell *et al.*, 1967; Moss and Siassi, 1970). Prevalence studies on congenital heart disease in schoolchildren exclude retarded children in whom the prevalence of congenital heart disease is greater than in the general population (Doyle and Rutkowski, 1970). Despite these limitations it was still considered worth while to assess the prevalence of congenital heart disease during a survey on rheumatic heart disease (McLaren *et al.*, 1975) in black schoolchildren of the South Western Townships of Johannesburg (Soweto).

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Subjects and methods

Details of the Soweto population and sampling technique have been previously described (McLaren *et al.*, 1975). In 1972, a stratified random sample of 12 050 children was drawn from a total Soweto school population of 99 000. An age range of 2 to 18 years was obtained and the age distribution was as follows: 2 to 6 years (21 %); 7 to 10 years (29 %); 11 to 14 years (35 %); and 15 to 18 years (15 %). The number of boys and girls was equal.

The children were screened at the schools or crèches by a team of 10 doctors, 5 of whom were experienced cardiologists and the remainder of whom had all received at least 6 months training in this cardiac unit. Three observers, at least one of whom was a senior cardiologist, were present at each session. All children were examined initially by one observer, but if organic heart disease was suspected or detected the child was then 'recirculated' (McLaren *et al.*, 1975) to the other 2 observers who were unaware that the child had been previously examined and 3 independent and unbiased assessments were thus obtained. At the end of each session such children were again examined by the 3 observers and all had to agree that organic heart disease was present before the final positive diagnosis could be accepted. Electrocardiograms and blood pressure examinations were performed on these children and they were referred to a cardiac clinic for chest radiographs and further management.

The relation of congenital heart disease to age, sex, educational level, and nutritional status was assessed. The practice of recirculation made possible a study of observer performance in the detection of congenital heart disease. The types of congenital heart defects are discussed but their numbers are too small to permit meaningful analysis of age and sex distribution. Statistical testing of associations was based on a χ^2 test.

Results

Congenital heart defects were detected in 48 of the total of 12 050 children. The optimally weighted estimate (Cochran, 1963) of the prevalence in the school population was 3·9 per 1000 with a 95 per cent confidence interval of ± 1·2. In all but one child, who had previously undergone surgery for closure of a ventricular septal defect, the diagnosis of congenital heart disease was made for the first time during the survey.

In crèche children aged 2 to 6 years, the prevalence was 2·95 per 1000, whereas in lower primary (first 4 school years) and higher primary (fifth to eighth school years), it was 3·31 and 4·74 per 1000, respectively (Fig. 1). The observed increase in prevalence with educational grade was not significant at the 5 per cent level. Similarly, there was no significant relation of congenital heart disease with age but the prevalence was less than that of rheumatic heart disease in the children 7 years of age and older (Fig. 2). The ratio of the prevalence rate in boys to that in girls was 1·42. The nutritional status of children with congenital heart disease was assessed as normal in 76 per cent, overnourished in 7 per cent, and undernourished in 17 per cent, whereas in children with normal hearts it was 86 per cent, 7 per cent, and 7 per cent, respectively.

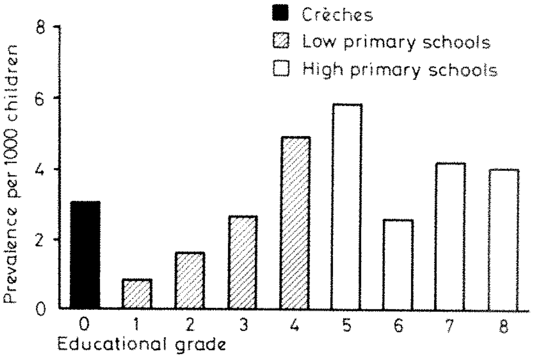

Fig. 1 *Prevalence of congenital heart disease in Soweto children of different educational grades.*

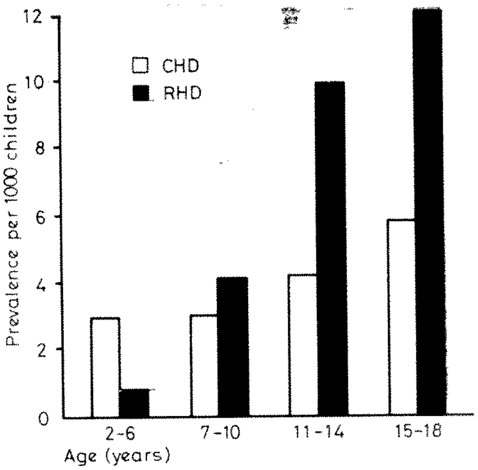

Fig. 2 *Age specific prevalence rates of congenital (CHD) and rheumatic (RHD) heart disease in 12 050 Soweto schoolchildren. The prevalence of CHD exceeds that of RHD in 2- to 6-year-old children only.*

Table 1 *Prevalence and distribution of specific congenital heart defects in Soweto children*

Type	*No. of children*	*Prevalence per 1000*	*Percentage of total congenital heart defects*
Ventricular septal defect	25	2·07	52·1
Atrial septal defect	5	0·42	10·4
Dextrocardia	5	0·42	10·4
Bicuspid aortic valve	2*	0·17	4·2
Pulmonary stenosis	2	0·17	4·2
Ebstein's anomaly	1	0·08	2·0
Isolated pulmonary regurgitation	8	0·66	16·7
Total	48	3·99	100·0

*In one child, there was an associated coarctation of the aorta.

SPECIFIC CONGENITAL HEART DEFECTS

The distribution of individual congenital heart defects in the children is shown in Table 1.

Ventricular septal defects

Of the 25 children with ventricular septal defects, 9 were boys, 15 were girls, and the sex of the remaining child was not recorded. In 20 children, the lesions were classified as very small ventricular septal defects characterised by a so-called 'atypical' (Van der Hauwaert and Nadas, 1961; Vogelpoel *et al.*, 1961; Barlow and Pocock, 1965) high pitched crescendo-decrescendo systolic murmur ending well before the second heart sound and heard best at the lower left sternal border. The remainder of the children with ventricular septal defects had pansystolic murmurs and the shunts were clinically assessed as small in 4 and moderate in 1.

Atrial septal defects

An ostium secundum defect was diagnosed in 4 children and an ostium primum defect in 1 child. In 2 of the children with ostium secundum defects, the shunt was assessed as moderate and both these children have since had surgical closure of these defects. In the remaining 3 children, the shunts were small.

Dextrocardia with situs inversus

Five children, 4 boys and 1 girl, had mirror-image dextrocardia with otherwise normal hearts. Vibratory systolic murmurs were present in 4. These children were of varying ages (5, 7, 10, 14, and 15 years) and from different geographical areas of Soweto.

Bicuspid aortic valves

The presence of a bicuspid aortic valve was suspected in 2 girls, aged 12 and 17 years. The 12-year-old girl had an ejection systolic murmur associated with an aortic ejection click. The 17-year-old had moderate aortic regurgitation but the additional signs of radio-femoral delay and hypotension in the lower extremities led to the diagnosis of an associated coarctation of the aorta.

Pulmonary stenosis

Pulmonary valvular stenosis was diagnosed in 2 girls, aged 11 and 15 years. In the latter child, the degree of stenosis was assessed clinically as moderate with a probable pressure difference across the pulmonary valve of about 40 mmHg.

Table 2 *Prevalence of congenital heart disease in school surveys*

Place	*Year of survey*	*Sample size*	*Initial screening method*	*Rate per 1000*	*Percentage not previously diagnosed*
Sydney (Stuckey *et al.*, 1957)	1955	34 863	School medical officers	2·8	?
Colorado (Maresh *et al.*, 1952)	?	10 948	Physicians	2·7	30
Chicago (Smith *et al.*, 1965)	1962	49 753	Tape recordings	1·4	42
Denver (Morton and Huhn, 1966)	1963	17 366	Duplicate physician examinations and tape recordings	4·6	45
Los Angeles (Durnin *et al.*, 1968)	1966	3797	Phonocardioscan* (computer); cardiologists (for 10% of sample)	3·6	50
Sacramento (Cayler and Warren, 1970)	1969	6625	Phonocardioscan* (computer); cardiologists (for 23% of sample)	5·1	27
Soweto (Present study)	1972	12 050	Cardiologists	3·9	98

*Portable analogue-digital computer by which heart sounds are analysed on a beat-by-beat basis.

Isolated pulmonary regurgitation

In 8 children, a short medium-pitched early diastolic murmur was present over the second left interspace and congenital mild pulmonary regurgitation was diagnosed (Baba *et al.*, 1974).

Ebstein's anomaly

One child, a 13-year-old boy, had the typical clinical, electrocardiographic and radiological features of Ebstein's anomaly (Pocock *et al.*, 1969).

OBSERVER PERFORMANCE

On recirculation of the 48 children in whom congenital heart disease had been detected by the first observer, the diagnosis was missed by one or both of the subsequent examiners in 11 children. Ventricular septal defects were missed in 5 children, an atrial septal defect in 1 child, dextrocardia in 2, and minor abnormalities of the pulmonary valve in 3.

Discussion

The prevalence of congenital heart disease in Soweto schoolchildren is in the upper part of the range of rates obtained in school surveys in other parts of the world (Table 2). However, caution is necessary when comparing rates in these studies because the methods of initial screening of the children differ. In some surveys, tape recordings (Smith *et al.*, 1965), computers (Durnin *et al.*, 1968; Cayler and Warren, 1970), or examinations by doctors with no specific training in cardiology were used though positive cases were later examined by cardiologists (Stuckey *et al.*, 1957; Morton and Huhn, 1966). In the Soweto survey, cardiologists performed the initial screening and therefore the detection rate was probably relatively increased. The practice of recirculation and independent triplicate examinations for all children with abnormal hearts reduced the yield of false positives and also observer bias. In South Africa, the absence of compulsory schooling for black children tends to exclude from the sample those children with more severe forms of congenital heart disease who would be less likely to be attending school. The case fatality rate of congenital heart disease in the first few years of life is probably high in this population because of the common practice of home deliveries and the high general infant mortality. The prevalence rate in the Soweto school population may, therefore, be an underestimate of the true prevalence in this community. It can nevertheless be concluded that the prevalence is at least as common as in white schoolchildren.

The distribution of the types of congenital heart disease, with a predominance of ventricular septal defects (Maresh *et al.*, 1952; Stuckey *et al.*, 1957; Morton and Huhn, 1966; Cayler and Warren, 1970), is similar to that reported in other school surveys. There were two unusual findings. Firstly, despite impressions that persistent ductus arteriosus is more common at high altitudes such as Johannesburg which is 6000 feet above sea level (Alzamora *et al.*, 1952; Bradlow *et al.*, 1964), no child with this defect was detected. A possible reason for this is that children in this population with an unoperated large persistent ductus arteriosus may have a high morbidity and mortality caused by increased pulmonary infections and cardiac failure superimposed on a background of low socioeconomic status and malnutrition. This does not explain the absence of children with small defects or of those who had had operations for closure of larger defects. However, the total number of positive cases was only 48 and was thus too small to permit reliable estimates of the prevalence of individual defects and conclusions thereof. Secondly, though the reported prevalence of dextrocardia is only 1 per 22 000 (Hollman, 1968), 5 children with this anomaly were detected in Soweto (1 per 2410) and all had situs inversus. The variation in age and geographical distribution did not suggest a clustering of cases with a common causation. Unfortunately it was not possible for us to obtain more detailed family histories. Again, this apparent high prevalence of situs inversus could represent a chance occurrence in a relatively small sample.

In contrast to other school studies (Table 2), the prevalence of previously undiagnosed congenital heart disease was high. The combined prevalence of previously undiagnosed congenital and rheumatic heart disease in Soweto schoolchildren was 9·37 per 1000 compared with a total prevalence of 10·8 per 1000. The large proportion of children with heart disease detected for the first time during this survey and the fact that rheumatic heart disease still exceeds the rate for congenital heart disease in all children over the age of 6 years are causes for concern about the availability and utilisation of quality health care for this community.

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How to determine atrial situs?

Considerations initiated by 3 cases of absent spleen with a discordant anatomy between bronchi and atria

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SUMMARY Three cases have been documented in which abdominal heterotaxy with absent spleen was accompanied by a discordant anatomy between the tracheobronchial tree and the atria. In 1 instance the tracheobronchial anatomy was as in situs inversus but the venous connections and the atrial appendages suggested situs solitus. The second case exhibited a situs solitus anatomy of the tracheobronchial tree, but the morphological features of the atria were mixed up in the sense that the venous connections and atrial septum suggested situs inversus, whereas the atrial appendages were of a right isomeric type. The third case was interesting in showing a symmetrical tracheobronchial tree not accompanied by isomeric atrial appendages. The latter and the atrial septum exhibited situs solitus characteristics, though the venous connections suggested 'situs ambiguus'. Such observations have led us to reconsider the criteria that determine the classification of atrial situs. It is our contention that in cases characterised by major abnormalities in atrial anatomy, particularly with respect to the venous connections, the prime feature for identification of atrial situs would be the morphology of the atrial appendages, which represent the 'true' atrial Anlagen. Positive identification of atrial appendages would also enable a more precise definition of the term 'atrial situs ambiguus'. This term can then be defined as the situs characterised by either bilateral right- or bilateral left-sided morphological characteristics of the atrial appendages, irrespective of the venous connections or atrial septal anatomy.

Identification of atrial situs is the initial step in any segmental analysis and classification of congenital heart malformations (Lev, 1954; Van Praagh *et al.*, 1964a; de la Cruz and Nadal-Ginard, 1972; Van Praagh, 1972; Kirklin *et al.*, 1973; Anderson *et al.*, 1974; Shinebourne *et al.*, 1976; Stanger *et al.*, 1977; Van Praagh, 1977).

According to Lev (1954) and Lev and Rowlatt (1961), identification of atria as either right or left should be based on morphological characteristics. However, since the anatomy of the atria is distorted in many cases of congenital heart disease, the clinical determination of atrial situs may pose a problem, particularly in the presence of heterotaxy of abdominal viscera or a discordance in situs between the abdominal and the thoracic organs. In these circumstances it has been suggested that atrial situs can be inferred from the configuration of the tracheobronchial tree (Landing *et al.*, 1971; Partridge *et al.*, 1975), since it is widely accepted that atrial situs corresponds with that of the thoracic organs (Van Praagh *et al.*, 1964a; Van Mierop *et al.*, 1970). Indeed, in patients with a normal spleen only 2 exceptions to this rule have as yet been reported (Clarkson *et al.*, 1972; Liberthson *et al.*, 1973; Brandt and Calder, 1977). However, anatomical studies have disclosed several other exceptions to this 'rule' in the presence of splenic abnormalities, albeit that the various authors do not always emphasise the discrepancy (Freedom and Fellows, 1973; Liberthson *et al.*, 1973; Freedom and Harrington, 1974; Anderson *et al.*, 1976). These exceptions necessitate a reconsideration of the criteria that determine the classification of atrial situs.

It is for this reason that we present 3 patients with absent spleen and discordant anatomy between bronchi and atria, in order to discuss one of the basic questions with respect to the segmental analysis of congenital heart disease, that is, how do we determine atrial situs?

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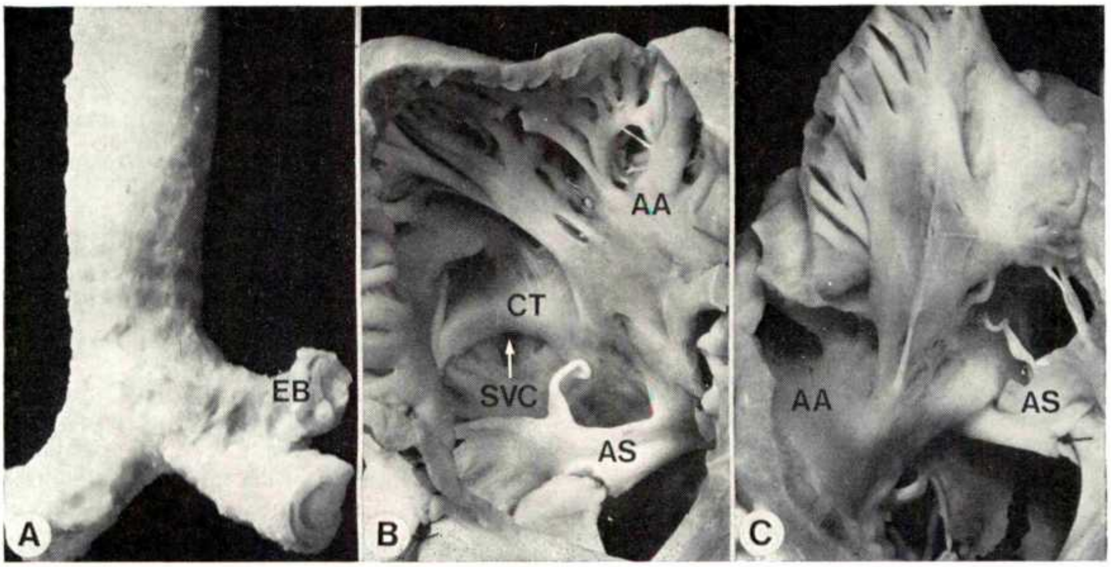

Fig. 1 *Case 1. (A) The tracheobronchial bifurcation viewed from* anterior. *There is an eparterial bronchus (EB) on the left. (B) The opened right-sided atrium; the atrial septum (AS) consists of a thin fenestrated band of endocardial tissue. There is a persistent common atrioventricular canal. The atrial appendage (AA) shows the internal arrangement of pectinate muscles and a crista terminalis (CT), as in a morphological right atrium. The superior caval vein (SVC) and inferior caval vein (not visible in this view) enter this right-sided atrium. (C) The opened left-sided atrium. The atrial appendage (AA) on this side shows the characteristics of a morphological left atrium. Note the deficient atrial septum (AS). The pulmonary veins which connected to this left-sided atrium are not visible.*

Case reports

CASE 1

A baby girl was admitted to hospital shortly after birth because of episodes of cyanosis. Clinical examination disclosed heterotaxy of the abdominal situs with oligaemic lung fields and laevocardia. The child died at 2 days of age with signs of severe hypoxia from heart failure.

The necropsy confirmed the presence of heterotaxy of the abdominal organs with a centrally positioned symmetrical liver. The spleen was absent. There was agenesis of the right kidney.

The main stem bronchus on the left was short with early origin of an upper lobe bronchus (Fig. 1A). The latter was classified as an eparterial bronchus since it ran 'above', dorsal to the upper lobe pulmonary artery. The right main bronchus looked like a normal left (Fig. 1A). The upper lobe bronchus, in this situation, ran 'below', ventral to the associated upper lobe artery; on which criterion it was identified as the hyparterial bronchus. The terms eparterial and hyparterial for bronchi will be used throughout this paper in their classical meaning, indicating the specific relation between bronchus and artery considered characteristic for right and left-sidedness, respectively. In other words, the anatomy of the bronchi in this case was reversed, suggesting a situs inversus anatomy of the thoracic organs. The right-sided atrial appendage was plump, showing an inner aspect characterised by coarsely arranged, heavy pectinate muscles extending into the apex, while the appendage communicated to the vein receiving part of the atrium through a wide opening, in part delineated by a ridge of muscle, the crista terminalis. The left-sided atrium, on the other hand, had a slender, finger-like external appearance, the inner aspect of which showed parallel arrangement of pectinate muscle not extending fully to the apex, while the appendage connected to the vein received part of the atrium through a relatively small opening without a crista terminalis. The external and internal anatomy of the atrial appendages thus suggested situs solitus, with the morphologically right atrial appendage on the right and the morphologically left atrial appendage on the left (Fig. 1B and C). The inferior caval vein ascended on the right side of the vertebral column to enter the right-sided atrium. There was a right-sided superior caval vein which entered the

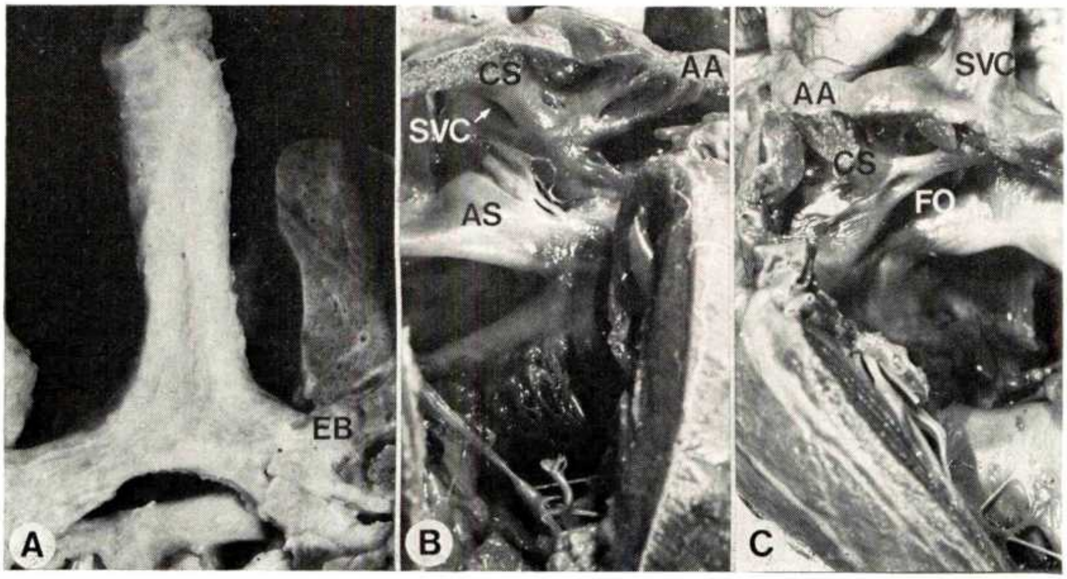

Fig. 2 *Case 2. (A) The tracheobronchial bifurcation viewed from* posterior. *There is an eparterial bronchus (EB) on the right. (B) The opened right side of the heart. The atrial appendage (AA) on this side shows the internal arrangement of a morphological right atrium. A crista supraventricularis (CS) separates the appendage from the main atrial chamber, which receives a right-sided superior caval vein (SVC) and the pulmonary veins (not visible in this view). The atrial septum (AS) has the septum primum on its right-sided aspect. Note the presence of a persistent common atrioventricular canal. (C) The opened left side of this heart. Again, the atrial appendage (AA) shows features of a morphological right atrium and a crista terminalis (CS). A superior (SVC) and inferior (not visible in this view) caval vein enters the left-sided atrium. The atrial septum at this side exhibits the fossa ovalis (FO).*

same atrium. The 4 pulmonary veins connected to the left-sided atrium in the usual way. The atrial septum was deficient and was represented only by a thin membrane with thread-like extensions (Fig. 1B and C). An indication of a limbus was present in the right-sided atrium. The right-sided atrioventricular connection was absent. The right atrium drained by way of a large atrial septal defect of the primum type to the left-sided atrium. The latter connected to a univentricular heart of right ventricular type which carried a minute trabecular pouch of left ventricular type in the posteroinferior wall. The aorta arose from the main chamber; there was pulmonary atresia and hypoplasia of pulmonary arteries fed from the aorta through a persistent tortuous ductus arteriosus.

CASE 2

A baby boy developed progressive cyanosis shortly after birth. Clinical examination revealed heterotaxy of the abdominal situs, characterised by a symmetrical liver and right-sided stomach. There was laevocardia and pronounced oligaemia of the lung fields. The findings were considered suggestive of the 'asplenia syndrome'. The child developed increasing cyanosis and dyspnoea and died at the age of 6 weeks.

Necropsy confirmed the presence of heterotaxy of the abdominal situs. The spleen was absent. The inferior caval vein ascended to the left of the vertebral column. The thoracic situs appeared normal with a right-sided trilobed lung and bilobed lung on the left. The tracheobronchial anatomy was that of situs solitus with an eparterial bronchus on the right and a hyparterial bronchus on the left (Fig. 2A). The atrial appendages, however, showed an isomeric morphology. Both appendages had the external appearance of a morphological right atrial appendage, an impression endorsed by the internal arrangement showing a crista terminalis on either side with pectinate muscles radiating from it (Fig. 2B and C). In other words a situs solitus morphology of the tracheobronchial tree was associated with a right-sided isomeric morphology of the atrial appendages. There was a right and left-sided superior caval vein, both connecting to the respective atria. The inferior caval vein connected to the left-sided atrium. Four pulmonary

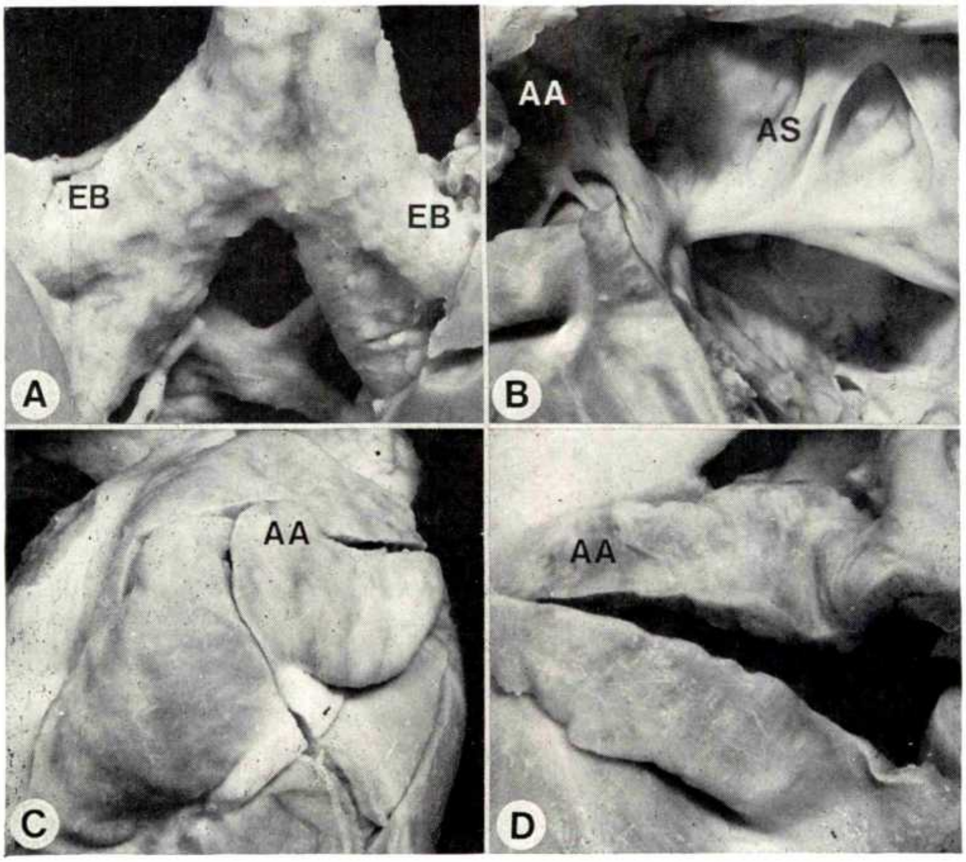

Fig. 3 *Case 3. (A) The tracheobronchial bifurcation viewed from* posterior. *There is an isomeric branching pattern, showing bilateral eparterial bronchi (EB). (B) The interior of the left-sided atrium. The atrial appendage (AA) has the features of a morphological left atrium; there is no crista terminalis. The atrial septum (AS) has the septum primum on the left-sided aspect. The pulmonary veins (not visible in this view) connected through a common vein to this left-sided atrium. Note the presence of a persistent common atrioventricular canal. (C) The exterior of the right-sided atrial appendage (AA), showing the characteristic shape of a morphological right atrium. (D) The exterior of the left-sided atrial appendage (AA) showing the characteristic shape of a morphological left atrium.*

veins connected to the right-sided atrium in an otherwise normal fashion. The 2 atria were separated by an interatrial septum which showed a large primum type defect as part of a persistent common atrioventricular canal of the complete type. The septal anatomy, however, still enabled identification of the limbus of the fossa ovalis on the left side and the septum primum on the right. The coronary sinus was absent. The right-sided atrium connected to a morphologically right ventricle and the left-sided atrium connected to a morphologically left ventricle. The aorta arose from the morphologically right ventricle in an anterior position; the pulmonary trunk was hypoplastic and showed an atretic pulmonary ostium, albeit in potential communication with the morphologically left ventricle.

CASE 3

A baby boy was admitted to hospital immediately after birth because of severe cyanosis. The child was in severe heart failure and died 10 hours after birth.

The necropsy showed heterotaxy of the abdominal organs with a central symmetrical liver and absent spleen. The inferior caval vein ascended on the right side of the vertebral column, but it stayed remote from the hepatic veins which had a separate connection to the atria of the heart (see below).

The tracheobronchial anatomy revealed a symmetrical bronchial branching pattern with bilateral eparterial bronchi (Fig. 3A). The atrial appendages, however, suggested a situs solitus anatomy with a right-sided atrial appendage showing the characteristics of a morphologically right atrial appendage and a left-sided atrial appendage with the characteristics of a morphologically left atrial appendage (Fig. 3B and C). The atrial septum, moreover, was formed as in situs solitus with the limbus of the fossa ovalis on the right side and the septum primum on the left (Fig. 3D). A large primum atrial septal defect was present, as part of a persistent atrioventricular canal of the complete type. A superior and an inferior caval vein connected to the atrium on the right, while a left-sided superior caval vein and the hepatic veins connected to the left-sided atrium. The pulmonary venous connection was abnormal in the sense that the 4 pulmonary veins were confluent behind the atria and then connected through a common vein to the left-sided atrium. The coronary sinus was missing. The 2 atria connected through a common atrioventricular canal with a univentricular heart of left ventricular type, which carried a small outlet chamber in its right anterior shoulder. The aorta arose from the outlet chamber; the pulmonary ostium was atretic. A right-sided tortuous ductus arteriosus connected the aorta to the pulmonary arteries.

Discussion

These 3 cases showed a discordancy between the anatomy of the tracheobronchial tree and the morphological features of the atria, though they were inconsistent among themselves (Fig. 4). These observations are of interest since identification of atrial situs is considered the primary step in sequential analysis and categorisation of congenital cardiac malformations (Lev, 1954; Van Praagh *et al.*, 1964a; de la Cruz and Nadal-Ginard, 1972; Van Praagh, 1972; Kirklin *et al.*, 1973; Anderson *et al.*, 1974; Shinebourne *et al.*, 1976; Stanger *et al.*, 1977; Van Praagh, 1977). In most patients with a congenital cardiac anomaly there will be no problem in this respect, since atrial situs will concur with visceral situs. However, there are two conditions in which identification of atrial situs may become difficult. These situations are encountered in patients with a discordancy between the abdominal and thoracic visceral situs and in patients with

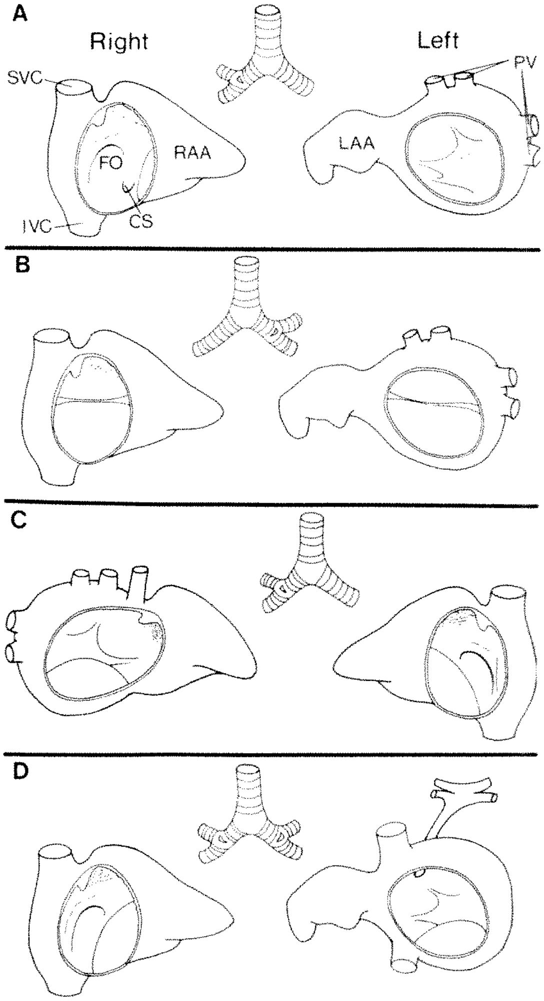

Fig. 4 *Diagrams of tracheobronchial anatomy and the morphological features that contribute to the identification of atrial situs. (A) The usual ('normal') condition. The tracheobronchial anatomy shows an eparterial bronchus on the right; a condition associated with 'situs solitus' of atria. The superior (SVC) and inferior (IVC) caval veins and the coronary sinus (CS) connect to the right-sided atrium, while the pulmonary veins (PV) connect to the left-sided atrium. The atrial septum exhibits the fossa ovalis (FO) on its right aspect, while the left side will show strand-like extensions of the septum primum. The right atrial appendage (RAA) is blunt ending, contains pectinate muscles, and is separated from the remainder of the right atrium by the crista terminalis. The left atrial appendage (LAA) is slender, 'finger-shaped', does not contain the coarse trabeculations that occur in the right atrial appendage, while a crista terminalis is absent. (B, C, and D) The various morphological features of the tracheobronchial tree and the atria are shown schematically as encountered in our cases 1, 2, and 3, respectively.*

heterotaxy of the abdominal organs. In these circumstances identification of tracheobronchial anatomy has gained much clinical favour (Landing *et al.*, 1971; Partridge *et al.*, 1975), since it is generally accepted that atrial situs will concur with that of the thoracic organs (Van Praagh *et al.*, 1964a; Van Mierop *et al.*, 1970). Thus, in case of a situs solitus or situs inversus morphology of the tracheobronchial tree one may expect the atria to show a situs solitus or a situs inversus morphology, respectively. On the other hand, with a symmetrical bronchial branching pattern, so-called isomerism of the tracheobronchial anatomy, 'atrial isomerism', is to be expected, which in itself may predict the presence of a complex cardiovascular anomaly (Van Mierop *et al.*, 1970, 1972a, b).

In patients with a normal spleen it thus far has only once specifically been stated that the tracheobronchial anatomy and that of the atria were not in accord. The initial report of this patient by Clarkson and associates (1972) documented situs solitus anatomy of the abdominal viscera, associated with dextrocardia, but with inverted anatomy of the atria and atrioventricular discordance. In a subsequent report, Brandt and Calder (1977) specifically stated that the tracheobronchial anatomy was as in situs solitus, that is in accord with that of the abdominal viscera, while the atria showed situs inversus. The latter conclusion was based on the morphology of atrial appendages and the systemic and pulmonary venous connections. Another patient with normal spleen, solitus anatomy of the lungs, laevocardia, and inversus anatomy of atria and abdominal viscera has been reported by Liberthson and co-workers (1973; case 9). However, these authors did not specifically state the bronchial branching pattern in this case.

More exceptions have been described in patients *with* splenic abnormalities, a condition from which major abnormalities of visceral situs can be predicted (Ivemark, 1955; Van Mierop *et al.*, 1972a, b; Freedom and Fellows, 1973; Stanger *et al.*, 1977). However, the tendency towards a symmetrical development of otherwise unpaired organ systems, which is considered characteristic for these conditions, does not necessarily always occur. In other words, a splenic anomaly is not always accompanied by symmetry of the thoracic organs (Towers and Middleton, 1956, case 1; Lev *et al.*, 1971, cases 7 and 8; Liberthson *et al.*, 1973, cases 1, 4, 12, 16, 19, 25, 29; Rose *et al.*, 1975, 3 cases), and when such isomerism of the tracheobronchial branching pattern is present this is not always associated with symmetry of the atria (Freedom and Fellows, 1973, cases 4, 5, 6; Liberthson *et al.*, 1973, cases 2, 3, 5; Freedom and Harrington, 1974, case 1; Anderson *et al.*, 1976, case 2). Two of our cases (cases 1 and 3), in this respect, endorse previous observations. Our second case is exceptional since it presented a situs solitus anatomy of the tracheobronchial tree, while the atrial appendages showed a morphologically right isomerism. As far as we are aware no cases have as yet been documented of absent spleen with a situs solitus branching pattern of the tracheobronchial tree and isomerism of atrial appendages. The case exemplifies that even in patients with absent spleen recognition of the tracheobronchial anatomy may not always lead to a proper classification of the situs of atria. Of course, the clinical usefulness of the tracheobronchial anatomy as a guide to the classification of atrial situs is by no means invalidated by these observations. They merely underline the fact that a 'rule' cannot be applied as 'law'.

These observations, therefore, necessitate a reconsideration of the criteria employed to identify atrial situs and they raise questions with respect to the terminology to be used.

IDENTIFICATION OF ATRIAL SITUS

The identification of atrial situs depends on a definite recognition of the cardiac chambers as either right or left, itself based on morphological criteria (Lev, 1954; Lev and Rowlatt, 1961). These are the connections of the systemic and pulmonary veins, the anatomical characteristics of the atrial septum, and the external and internal morphology of the atrial appendages. The significance of the atrial septum in identifying atrial situs can be considered of little *clinical* value, since the anatomical characteristics are not easily recognisable. The value of the venous connections is debatable since these are variable, particularly in congenital heart malformations accompanied by abnormalities in visceral situs. However, the venous connections have the major impact upon the clinical profile of the case and are more likely to be assessed within a clinical setting than is the morphology of the atrial appendages. Indeed, the connection of the inferior caval vein to the atria has been propagated as a reliable and readily obtainable guide to identify the morphologically right atrium in situs solitus and inversus situations (Kirklin *et al.*, 1973; Brandt and Calder, 1977). Our 3 cases seem to support this concept, since the inferior caval vein connected to an atrium which had other characteristics of a morphological right atrium, except that in 1 instance (case 2) the contralateral atrial appendage also showed characteristics of a morphological right atrium. However, it is well known that the course of the inferior caval vein can be abnormal, particularly in cases accompanied by multiple spleens

(Moller *et al.*, 1967). It is for this reason that we favour a more fundamental approach to the problem of identifying 'right' and 'left' morphological characteristics of atria. As initially suggested by Lev (1954), the basic nature of the atrium, being right or left, will be disclosed by the morphology of its appendage. Strictly speaking, the appendages represent the 'true' atria, while the major part of the definitive atrium is formed by secondary uptake of either sinus venosus tissue or pulmonary veins. One could argue that the anatomy of the atrial appendages has no bearing on the clinical significance of the case and, therefore, should not be promoted as the prime feature for atrial identification. This may be so, but the cases documented in this report exemplify the need for a criterion enabling identification of the 'true' atrial situs in all instances and not dependent upon the venous connections or morphology of the atrial septum. For instance, the first case in our series had a situs inversus anatomy of the tracheobronchial tree, but the venous connections and the morphology of the atrial appendages indicated 'situs solitus'. Should this case be classified as total anomalous systemic and pulmonary venous connections just because the tracheobronchial anatomy suggests situs inversus? We consider this case as an example of 'atrial situs solitus', with a discordant tracheobronchial anatomy taking the morphology of the atrial appendages as the major guide. The second case is of particular interest because the situs solitus morphology of the tracheobronchial anatomy was not in accord with any of the anatomical characteristics which determine atrial situs. Moreover, among themselves these characteristics were in contradiction, since the venous connections and the atrial septum suggested 'situs inversus' but the atrial appendages showed an isomeric right atrial morphology. What determines atrial situs in this case? The clinician diagnosed the atria as having a situs inversus morphology, which he based on the catheter studies. These investigations were carried out over 10 years ago and at that time no particular attempts were made to visualise the tracheobronchial anatomy. However, if this had been attempted before the catheter studies, it seems most likely that an erroneous suggestion of 'situs solitus' would have been forwarded. The necropsy disclosed the isomeric right atrial morphology of the appendages, in itself a common condition in cases of 'asplenia'. In accordance with previous statements we consider that the morphology of the atrial appendages is the final denominator of atrial situs and we, therefore, classify this case as having 'atrial situs ambiguus'. The latter term is then used in the sense of a symmetrical morphology of the atrial appendages, irrespective of the appearance of other criteria for atrial situs.

What to do with the third case, which had bilateral right-sided morphology of the tracheobronchial tree? From this observation 'atrial isomerism' might be expected. However, the atrial appendages did not show a symmetrical morphology. Instead, the right-sided appendage showed characteristics of a morphological right appendage, and the left-sided one showed features of a morphological left appendage, suggesting 'situs solitus'. This supposition was further supported by the morphology of the atrial septum, with a limbus of the fossa ovalis on the right side. However, the venous connections were highly suggestive of 'atrial situs ambiguus', as recently defined (Shinebourne *et al.*, 1976). The case therefore exemplifies the need for a fundamental and pure approach to the classification of situs, particularly when the morphological features among themselves are not in agreement. For reasons outlined above we would like to promote the morphology of the atrial appendages as the prime feature in the identification of atrial anatomy and, hence, for the identification of atrial situs. We do not think that the complexity of atrial anatomy in itself justifies categorisation of atria within a certain type of situs. The terms 'situs ambiguus' and 'situs indeterminatus', in this respect, need further specification.

TERMINOLOGY OF ATRIAL SITUS

The term 'situs ambiguus' was introduced by Van Mierop *et al.* in 1970 to indicate, 'that in many patients with asplenia or polysplenia syndrome, the visceral situs cannot be determined because of symmetrical development of normally asymmetrical organs'. Van Mierop, on many occasions, has pointed out that the atria in these conditions cannot be classified as either right or left on anatomical criteria, since *both* atria show characteristics of either a right *or* a left atrium (Van Mierop *et al.*, 1964, 1972a, b). He coined the term 'isomerism' to indicate the symmetrical appearance of the atrial appendages under these circumstances (Van Mierop *et al.*, 1964), while other investigators employed the terms 'uncertain' (Van Praagh *et al.*, 1964b) or 'indeterminate' (Lev *et al.*, 1968; Liberthson *et al.*, 1973). The latter observers used the term 'indeterminate' for the situs of the atria when the atrial anatomy was highly abnormal, not necessarily associated with a symmetrical appearance of the atrial appendages. They stated that when the venous connections were highly abnormal and the atrial septum deficient one could not be sure of the situs, irrespective of the anatomy of the atrial appendages. Though under those circumstances they considered a 'presumptive diagnosis' of atrial situs, they actually never went so far as to use the morphology of the atrial appendages as a decisive feature for the classification of atrial situs in these complex malformations. In hearts with 'isomerism' of atrial appendages they consequently also use the term 'indeterminate' for atrial situs since situs could not be determined with certainty. Van Mierop, on the other hand, claimed that the morphology of the atrial appendages always enabled their identification, and it was for this reason that he preferred the term 'isomerism' instead of 'indeterminate' (Van Mierop *et al.*, 1964).

Recently, the term 'situs ambiguus' for atria has been proposed (Shinebourne *et al.*, 1976). The authors state that in this situation, 'it is not possible to identify separate right *and* left atria on morphological criteria. Thus, a common atrial chamber receiving both systemic and pulmonary venous returns is usually associated with bilateral right or left auricular appendages'. We have inferred from this description that the authors use the term also to include conditions in which such a common atrial chamber is present, but not necessarily associated with symmetry of the atrial appendages. Such a definition of 'situs' in our opinion is unfavourable since it permits various interpretations and does not limit itself to the indication of 'situs' but also encompasses additional anomalies. This introduces vagueness where one should be striving for clarity.

When we consider that the morphology of the atrial appendages can always be determined, and as far as we are informed also in a clinical setting, then the term 'situs ambiguus' for atria can be used in a more precise way. Positive identification of the morphology of the atrial appendages will narrow the number of possibilities for atrial situs to 4. First, there may be situs solitus, with the right atrial appendage on the right and the left atrial appendage on the left. Conversely, there may be situs inversus showing the 'inverted' pattern. Finally, there can be a symmetrical morphology of the atrial appendages, for which the term 'isomeric' seems most appropriate, which can be of either a bilateral right or a bilateral left-sided type. We suggest that the term 'atrial situs ambiguus' be used for those specific conditions only. In other words, the term 'atrial situs ambiguus' is not based upon non-identification, but on pertinent recognition of atrial morphology instead. For a precise description of the type of situs ambiguus one should then indicate whether it is of a bilateral right or a bilateral left-sided characteristic.

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Evaluation of thallium-201 exercise scintigraphy in coronary heart disease

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SUMMARY Thallium-201 myocardial imaging provides a non-invasive technique in the investigation of patients with suspected coronary heart disease. This study was designed to evaluate thallium-201 (^{201}Tl) scintigraphy in predicting the presence or absence of coronary heart disease in 50 patients presenting with chest pain.

^{201}Tl scintiscans were obtained in 4 projections at rest and on symptom-limited maximal exercise. The presence or absence of regional perfusion abnormality was determined by semiquantitative computer analysis. The results were compared with resting and exercise electrocardiography and the final diagnosis established by coronary arteriography.

In 33 patients with significant coronary artery disease, perfusion defects were present at rest in 13 (39%) and on exercise in 30 (91%). Exercise ^{201}Tl scintigraphy was significantly more sensitive in detecting the presence of coronary artery disease than resting scintigraphy. In 17 patients with normal coronary vessels, ^{201}Tl scans were normal in 15 at rest and 14 on exercise.

In 33 patients with coronary artery disease the electrocardiogram at rest and/or exercise was abnormal in 25 (76%). The combination of exercise ^{201}Tl scintigraphy and exercise electrocardiography identified all 33 patients subsequently shown to have significant coronary artery disease.

Seventy-one vessels in 33 patients were diseased. All regions with relative perfusion abnormality were supplied by diseased vessels. However, 21 of 71 diseased vessels (31%) were not associated with perfusion defects. This occurred only in patients with $\geqslant$ 2 vessel disease.

These results suggest that computer analysed ^{201}Tl exercise scintigraphy is a valuable technique for identifying patients with significant coronary artery disease. ^{201}Tl image data were highly sensitive for detecting the presence of coronary artery disease though accuracy in predicting the extent of disease was limited in patients with multiple vessel disease. These data provide further justification for the use of exercise ^{201}Tl scintigraphy especially in conjunction with exercise electrocardiography in the investigation of patients with chest pain.

Exercise testing has an established place in the investigation of patients with suspected coronary heart disease. However, the electrocardiographic response to exercise has limited diagnostic accuracy (Mason *et al.*, 1967; Kassebaum *et al.*, 1968; Roitman *et al.*, 1970; Blomqvist, 1971; Friesinger and Smith, 1972; Martin and McConahay, 1972; Borer *et al.*, 1975).

Myocardial imaging after the intravenous injection of thallium-201 (^{201}Tl) provides a non-invasive assessment of myocardial perfusion (Strauss *et al.*, 1975) and can be used to detect myocardial infarction (Wackers *et al.*, 1975; Parkey *et al.*, 1976; Hamilton *et al.*, 1977; Henning *et al.*, 1977; Wackers *et al.*, 1977) and stress-induced ischaemia (Bailey *et al.*, 1977; Lenaers *et al.*, 1977; McLaughlin *et al.*, 1977; Ritchie *et al.*, 1977; Rosenblatt *et al.*, 1977).

This study was designed to evaluate ^{201}Tl scintigraphy in predicting the presence or absence of coronary artery disease in patients presenting with chest pain. ^{201}Tl scintiscans were obtained at rest and after maximal exercise testing and the results compared with selective coronary arteriography.

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Patients and methods

Fifty patients being investigated for suspected coronary artery disease were studied. Forty-six patients were men and 4 were women, mean age 46·7 years ± 1·13 (mean ± SEM) range 27 to 57 years. ^{201}Tl scintiscans were obtained at rest and after exercise testing, with an interval of at least 5 days between rest and exercise studies. Both rest and exercise studies were performed within 14 days of coronary arteriography. The experimental nature of the study was explained and informed consent obtained.

RADIONUCLIDE STUDIES

Thallium-201 scintiscans were obtained at rest and after symptom limited maximal exercise testing.

EXERCISE TESTING

Continous multistage exercise was performed using a graded bicycle ergometer with initial workload of 300 kpm/min and increments of 300 kpm/min at 3-minute intervals. The electrocardiogram (modified V5 electrode) was monitored continuously with sampling at 3-minute intervals and at the end-point of exercise. The tests were discontinued because of chest pain (94%) or dyspnoea/fatigue (6%). Electrocardiographic monitoring and intermittent sampling was continued up to 12 minutes after exercise.

The exercise electrocardiogram was interpreted independently without knowledge of ^{201}Tl scintiscan or arteriogram results. The test was considered positive for the presence of coronary artery disease where there was horizontal or downsloping ST depression more than or equal to 1 mm during or after exercise.

In addition to the results of exercise electrocardiography, the presence of a previous myocardial infarction in the resting electrocardiogram, irrespective of the exercise electrocardiographic appearance, was considered to indicate the presence of coronary artery disease.

MYOCARDIAL IMAGING

Scintiscans were obtained after the intravenous injection of 2 mCi thallium-201 (thallous chloride, supplied by Duphar Laboratories). After a 4-hour fast, the rest injection was given in the upright position to minimise hepatic and gastric activity. The exercise injection was given at the onset of symptoms and exercise was terminated 30 seconds thereafter.

Myocardial imaging was performed using an Ohio Nuclear Series 100 Gamma Camera with a high resolution, medium sensitivity, parallel hole collimator. Scans were obtained in the anterior, 30° and 60° left anterior oblique, and left lateral projections. The gamma camera was interfaced to a Varian 620L computer and the image data stored on magnetic tape for later retrieval. The images were analysed using a semiquantitative technique to examine regions of interest (McKillop *et al.*, 1978; Murray *et al.*, 1978). Using the light pen of the computer, regions of interest were generated on each myocardial image corresponding to the anatomical areas described by Lenaers *et al.* (1977). The total counts in each region and its area were calculated by the computer and thus count density (counts per unit area) for each region were obtained. In each image, the maximal count density was scored as 100 per cent and the count density in the remaining regions in the same image expressed as a percentage of this. A study of normal volunteer subjects (McKillop *et al.*, 1978; Murray *et al.*, 1978) had indicated that count densities for given anatomical areas varied by less than 15 per cent. Thus a variation of 20 per cent or more was accepted as indicating abnormal perfusion.

Loci of hypoperfusion were attributed to vessel disease according to the data of Lenaers *et al.* (1977). Thus perfusion defects in the anterior, anteroseptal, and anterolateral regions were interpreted as indicating disease of the left anterior descending coronary artery and defects in the posterolateral region as indicating disease of the left circumflex coronary artery. Since the size of supplying areas of the right and left circumflex coronary arteries is dependent on the type of coronary circulation (Kalbfleisch and Hort, 1977), perfusion defects in the inferior and posterior areas were interpreted as indicating right and/or left circumflex disease. Hypoperfusion in the posteroseptal region was interpreted as indicating disease of the left anterior descending and/or right coronary arteries. Significant perfusion defects of the apical segment were considered as indicating the presence of coronary artery disease but could not be attributed to disease of a particular coronary artery.

CORONARY ARTERIOGRAPHY

Selective coronary arteriography was performed by the percutaneous femoral route. Significant coronary artery disease was considered present in any vessel where the luminal diameter was reduced by 50 per cent or more in any of the standard projections. For the purposes of this study, the right coronary artery, main left coronary artery, left anterior descending, and left circumflex coronary arteries were analysed. Patients with coronary artery disease were classified as

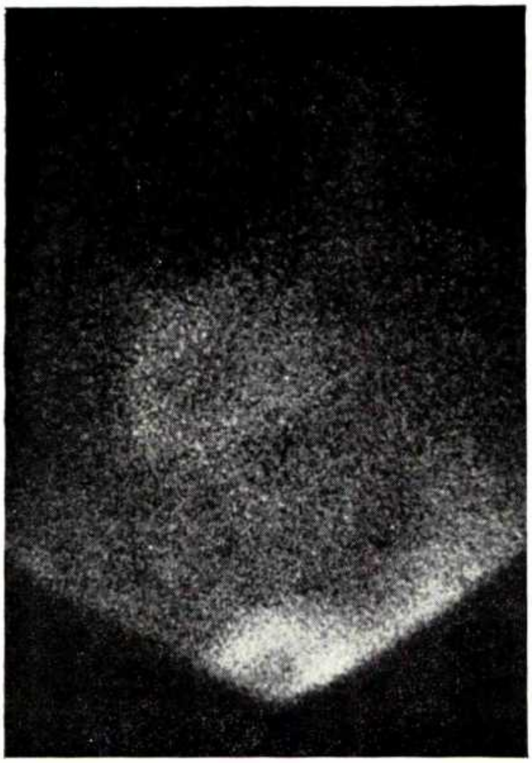

Fig. 1 *Thallium-201 rest scintiscan taken in 60° left anterior oblique projection in patient with normal left ventricular function and isolated left anterior descending artery disease. Nuclide density is equal in all areas in rest scan.*

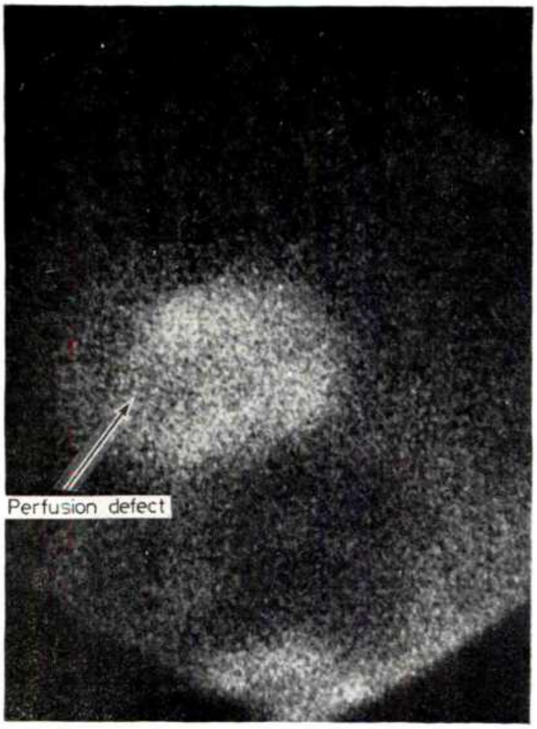

Fig. 2 *Thallium-201 exercise scintiscan taken in 60° left anterior oblique projection in same patient as Fig. 1. Note development of perfusion defect (arrowed) in anteroseptal and apical zones corresponding to left anterior descending artery disease.*

having single, double, or triple vessel disease according to the results of arteriography.

Results

RADIONUCLIDE STUDIES

Satisfactory scintiscans were obtained in all patients. Perfusion defects were present at rest in 15 patients and on exercise in 33 patients. In 10 of the 15 (67%) patients with resting defects, the distribution of perfusion abnormality was more extensive after exercise.

Typical image data are represented in Fig. 1 and 2. These scans were obtained in the 60° left anterior oblique projection in a patient with isolated left anterior descending artery disease and normal left ventricular function. Fig. 1 represents the rest scan and Fig. 2 represents the exercise scan. Nuclide density is equal in all areas in the rest scan; however, on exercise, a perfusion defect (arrowed) has developed in the anteroseptal and apical zones corresponding to left anterior descending artery disease.

ANGIOGRAPHIC DATA

Thirty-three patients had significant coronary artery disease, while 17 patients had normal vessels or minor (<50%) disease. Six patients had single vessel disease (3 right coronary artery; 3 left anterior descending artery); 16 double vessel disease (9 right coronary artery + left anterior descending artery; 4 left anterior descending + left circumflex arteries; 3 right coronary + left circumflex arteries; and 11 had triple vessel disease (left anterior descending + right coronary artery + left circumflex artery). Left main and isolated left circumflex disease were not encountered.

ELECTROCARDIOGRAPHIC DATA

In 25 of the 33 patients with arteriographic coronary artery disease, the electrocardiogram either at rest (12 patients) or on exercise (13 patients) indicated coronary disease. In those 12 patients with evidence of previous myocardial infarction on the electrocardiogram, 8 were located anteriorly and 4 inferiorly. In 13 patients significant ST abnormality developed on exercise.

Table *Relation between scintigraphic findings and distribution of vessel disease in 33 patients with coronary artery disease*

Vessel	*Frequency diseased*	*Perfusion defect present**	*Perfusion defect absent*	
			Normal scan	*Abnormal scan*
Right coronary artery	26	19	3	4
Left anterior descending	27	20	3	4
Left circumflex	18	11	2	5
Total	71	50	21 (31%)	

*Perfusion defect on exercise scintiscan.

COMPARISON OF DATA

In the 33 patients with significant coronary artery disease, perfusion defects were present in the rest ^{201}Tl studies in 13 patients (39%) and in the exercise ^{201}Tl studies in 30 patients (91%). Perfusion defects suggesting the presence of coronary artery disease were significantly more frequent in the exercise study than in the rest study (30 patients—exercise study; 13 patients—rest study; $P < 0\cdot05$). Three patients, 2 with triple vessel disease and 1 with double vessel disease (right coronary artery + left anterior descending artery), appeared to have normal ^{201}Tl studies at rest and exercise.

In the 17 patients with normal coronaries or minor disease, the ^{201}Tl scans were normal at rest in 15 and on exercise in 14. Two patients with normal coronary arteries had perfusion defects at rest, one of which persisted on exercise, and a further 2 patients developed perfusion defects on exercise. In 2 of these 3 patients with normal coronaries but abnormal exercise scintiscans the exercise electrocardiogram was also abnormal.

Six patients had single vessel disease, 16 had double vessel disease, and 11 triple vessel disease. The right coronary artery was involved in 26, left anterior descending in 27, and left circumflex in 18 instances. In 30 of the 33 patients with coronary artery disease, ^{201}Tl perfusion defects were present on exercise. In all instances, regions with relative underperfusion were supplied by diseased vessels. However, 21 of the 71 (31%) diseased vessels were not associated with perfusion defects (Table). Exercise scintiscans were normal in 3 patients despite the presence of triple vessel disease in 2 and double vessel disease in 1 (right coronary artery + left anterior descending). In 10 of the 30 patients (33%) with abnormal scintiscans and coronary artery disease, the distribution of perfusion abnormality underestimated the extent of disease. Eight of these patients had triple and 2 had double vessel disease. Thus, even where scintiscans were abnormal, 13 of 63 diseased vessels (21%) were not associated with the development of perfusion defects on exercise (Table). Image data underestimated left circumflex disease more frequently than right coronary artery and left anterior descending artery disease.

The electrocardiogram detected significant coronary artery disease in 25 of 33 patients (76%) with coronary artery disease; 12 had evidence of previous myocardial infarction and 13 had positive exercise electrocardiograms. The exercise scintigram was abnormal in 91 per cent of patients with coronary artery disease. In all the 3 patients with normal scintiscans and coronary artery disease, the exercise electrocardiogram was positive. Thus, the combination of electrocardiography and exercise scintigraphy suggested the presence of coronary artery disease in all 33 patients subsequently shown to have significant disease (Fig. 3).

Discussion

Increasing emphasis is being placed upon non-invasive techniques to identify patients with significant coronary artery disease, and resting and exercise electrocardiography are useful in the

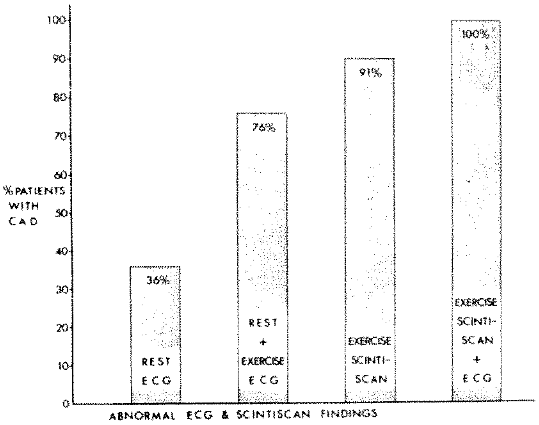

Fig. 3 *Frequency of abnormal electrocardiogram and exercise scintiscan findings in 33 patients with arteriographically documented coronary artery disease.*

investigation of patients with chest pain. However, both the resting Q wave (Horan *et al.*, 1971; McGuiness *et al.*, 1976) and exertional ST displacement (Mason *et al.*, 1967; Kassebaum *et al.*, 1968; Roitman *et al.*, 1970; Blomqvist, 1971; Friesinger and Smith, 1972; Martin and McConahay, 1972; Borer *et al.*, 1975) have limited accuracy in the detection of coronary artery disease. Lead selection may influence the performance of the exercise electrocardiogram. However, Blackburn (1969) showed that a modified V5 lead system was as accurate as the 12 lead electrocardiogram and the Frank XYZ leads in detecting exercise-induced ST segment displacement.

Myocardial imaging after the intravenous administration of radionuclide tracers provides a relatively non-invasive technique for estimating regional myocardial perfusion (Strauss *et al.*, 1975). Of the currently available tracers, ^{201}Tl appears to be one of the most promising and ^{201}Tl scintigraphy is proving useful in detecting myocardial infarction (Wackers *et al.*, 1975; Parkey *et al.*, 1976; Hamilton *et al.*, 1977; Henning *et al.*, 1977) and stress-induced ischaemia (Bailey *et al.*, 1977; Lenaers *et al.*, 1977; McLaughlin *et al.*, 1977; Ritchie *et al.*, 1977; Rosenblatt *et al.*, 1977).

This study shows that image data from ^{201}Tl exercise scintigraphy can be useful in predicting the presence or absence of coronary artery disease in patients presenting with chest pain. Abnormal image data were obtained in 30 of 33 patients (91%) with documented coronary artery disease ($\geq 50\%$ stenoses). Only 3 patients with coronary artery disease had normal image data. There were no apparent features to identify those 3 patients with normal scintiscans (1 with double and 2 with triple vessel disease) from those in whom perfusion defects developed. The high sensitivity of myocardial imaging in this study (91%) compared with other published data (Bailey *et al.*, 1977; McLaughlin *et al.*, 1977; Ritchie *et al.*, 1977) may be, in part, related to the technique of analysis. The visual assessment of myocardial images is open to several criticisms. Interpretation may be complicated by a relatively poor target—background ratio. Non-homogeneity of tracer uptake by the myocardium, particularly in the region of the apex (Cook *et al.*, 1976) may add further difficulties while the use of background subtraction and contrast enhancement techniques may serve to emphasise normal variations in tracer concentration rather than to disclose abnormal nuclide distribution. In addition, visual interpretation is subject to unintentional observer bias (Trobaugh *et al.*, 1978), though this may be eliminated by independent reporting of the image data by 2 or more observers with a consensus being accepted. In an attempt to overcome some of these difficulties a semiquantitative approach using a regions of interest technique was employed in the analysis of the image data. Our earlier study of normal subjects had indicated that count densities calculated for given anatomical areas varied by less than 15 per cent. Thus, a variation of 20 per cent or more in any area was accepted as indicating abnormal perfusion. The locus of abnormality was related to vessel disease as suggested by Lenaers *et al.* (1977). In view of the reciprocal relation between the size of area supplied by the right and left circumflex coronary arteries depending on the type of coronary circulation (Kalbfleisch and Hort, 1977), it was felt justified in accepting abnormal perfusion in inferior and posterior segments as indicating disease of right and/or left circumflex vessels. The approach is not, however, wholly objective since it requires a selection of regions of interest by the observer with the attendant risk of interobserver variation and is only semiquantitative since count densities for any given anatomical area will be influenced to some extent by activity present in adjacent partially overlapping areas and by background activity.

Rest imaging was significantly less useful in detecting the presence of myocardial ischaemia than was the exercise data (exercise sensitivity 91%; rest sensitivity 39% $P < 0{\cdot}05$). However, blood flow and regional distribution abnormalities caused by coronary stenoses of 50 per cent or more may only become apparent during exercise or pharmacological challenge (Gould *et al.*, 1974a, b). Thus, since myocardial ^{201}Tl distribution parallels flow (Strauss *et al.*, 1975), it might be expected that resting image data may not detect haemodynamically significant coronary disease.

The group of patients with normal coronary arteries or minor disease was small, predominantly male, and, since the presenting symptom in each was chest pain, cannot be classed as 'normal'. However, perfusion defects on ^{201}Tl exercise scintigraphy proved specific for the presence of coronary artery disease in all but 3 patients (specificity 82%). Two of these patients also had an 'ischaemic' response to exercise on the electrocardiogram and may fall into the category of patients with angina but without arteriosclerotic coronary disease (Likoff *et al.*, 1967; James, 1970; Waxler *et al.*, 1971; Bemiller *et al.*, 1973; Kemp *et al.*, 1973).

The exercise ^{201}Tl scintigram could detect the presence of myocardial ischaemia and the location of perfusion defect corresponded to a diseased vessel. However, though accurate in detecting the presence of coronary artery disease in a given patient, this does not imply accuracy in predicting the extent of disease. A total of 31 per cent (21 of 71) diseased vessels were not associated with appropriate perfusion defects. This was encountered in 13 of the 33 patients with coronary artery disease, 10 of whom had triple vessel and 3 with double vessel disease. Several explanations can be proposed. A perfusion defect was defined by comparing regional tracer concentrations. The region with the highest count density was accepted as 'normal', but may well have been supplied by a vessel with significant luminal narrowing. This is particularly apposite in patients with multiple vessel disease. Further, the development of ischaemia in only one of a number of potentially ischaemic zones may have produced image data underestimating the extent of disease, while the contribution of coronary collateral circulation may have influenced the regional concentration of tracer. Circumflex disease was most frequently underestimated. This is possibly related to regional overlap in the scanning projections used. Only in the 60° left anterior oblique projection is an isolated region (posterolateral) supplied by the left circumflex clearly visualised. However, it should be emphasised that the ^{201}Tl image data were highly sensitive (91%) for detecting the presence of coronary artery disease despite the limited accuracy in predicting the extent of disease.

The combination of rest and exercise electrocardiography detected the presence of coronary artery disease in 76 per cent of patients with coronary artery disease. Exercise imaging compares favourably—91 per cent scintigram positive. However, sensitivity for the presence of coronary artery disease was 100 per cent when both the exercise scintigram and electrocardiogram were taken into account (Fig. 3).

These results suggest that computer analysed ^{201}Tl imaging was a useful additional technique in the investigation of patients with suspected coronary artery disease. Perfusion defects on the exercise scintigram were sensitive, but slightly less specific for the presence of coronary artery disease. These data provide further justification for the use of exercise ^{201}Tl scintigraphy especially in conjunction with exercise electrocardiography in the investigation of patients presenting with chest pain.

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Thallium-201 scintigraphy in diagnosis of coronary stenosis[1]

Comparison with electrocardiography and coronary arteriography

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SUMMARY The sensitivity of rest and exercise thallium-201 scintigraphy for the detection of significant coronary artery disease and myocardial ischaemia was compared with rest and exercise electrocardiography in 46 patients with chest pain. Of 26 patients with greater than 70 per cent coronary stenosis, 16 had abnormal rest thallium-201 scintigrams and 13 had Q waves. Myocardial perfusion defects in the resting scintigram correlated very well with evidence of previous myocardial infarction (16 of 17 patients, 94%); significant Q waves were present in 13 of these 17 patients (76%).

After exercise, abnormal thallium-201 scintigrams consistent with ischaemia were found in 21 patients (81%). Abnormal exercise electrocardiograms were present in 15 patients (58%). The combination of abnormal exercise thallium-201 scintigrams or exercise electrocardiograms (23/26, 88%) exceeded abnormal exercise electrocardiograms alone (15/26, 58%). The two procedures were thus complementary. Abnormal rest or exercise thallium-201 scintigrams were obtained in 25/26 patients (96%) compared with abnormal rest or exercise electrocardiograms in 21/26 patients (84%). Twenty patients with less than 50 per cent coronary stenosis had normal rest thallium-201 scintigrams and no Q waves. Two had abnormal exercise thallium-201 scintigrams and 7 had abnormal exercise electrocardiograms. Thus, exercise thallium scintigraphy has higher sensitivity than exercise electrocardiography in detecting exercise induced ischaemia and is more specific. Scintigraphy appears to have a higher sensitivity than electrocardiography in detecting coronary artery disease.

While each of the patients with triple vessel coronary disease had positive exercise perfusion scintigrams and positive exercise electrocardiograms, the thallium-201 scintigram was more sensitive than the rest or exercise electrocardiogram in patients with single vessel disease.

The correlation of thallium perfusion defects at rest and/or exercise with angiographically significant coronary stenosis was higher for the left anterior descending and right coronary arteries than for the circumflex coronary artery.

Myocardial perfusion scintigraphy following the intravenous injection of radionuclides at rest and during peak exercise represents a non-invasive method for the diagnosis of haemodynamically significant coronary artery disease (Zaret *et al.*, 1973b).

The major determinant of the myocardial distribution of cationic tracers such as potassium-43 and thallium-201 is blood flow (Prokop *et al.*, 1974; Strauss *et al.*, 1975). Reduced tracer uptake at peak exercise but not at rest indicates transient myocardial ischaemia. Perfusion defects at rest which do not change with exercise are consistent with myocardial infarction, while rest defects associated with an increased perfusion defect with exercise are consistent with both previous infarction and myocardial ischaemia.

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Thallium-201 has generally replaced potassium-43 and rubidium-81 because it has an energy spectrum more favourable for imaging with currently available scintillation cameras, and a longer physical half-life (Bradley-Moore *et al.*, 1975). The thallium-201 scan has been reported to be more sensitive than the exercise electrocardiogram in patients with significant coronary artery disease (Bailey *et al.*, 1977; Ritchie *et al.*, 1977a, b; Botvinick *et al.*, 1978). The present study was undertaken (1) to evaluate rest and exercise thallium-201 myocardial perfusion imaging in the detection of significant coronary stenosis determined by coronary arteriography; (2) to compare the sensitivity of thallium-201 myocardial imaging with rest and exercise electrocardiography; and (3) to correlate the thallium-201 scintigram with the number of coronary arteries involved and with the location of significant coronary stenosis.

Subjects and methods

Forty-six patients with known or suspected coronary artery disease were studied. There were 39 men and 7 women, with a mean age of 56 years (range 35 to 74 years). Of the 46 patients, 17 had prior myocardial infarction documented by two or more of the following criteria: (a) typical history; (b) pathological Q waves (duration 0·04 s or greater); (c) characteristic serial enzyme changes (serum creatine kinase and/or aspartate transaminase (SGOT); (d) asynergy on left ventriculography. All patients had a history of chest pain suggestive of angina pectoris at the time of the study.

MYOCARDIAL PERFUSION IMAGING

Myocardial imaging was performed after exercise and at rest. Before starting the exercise study an indwelling catheter was inserted percutaneously into an antecubital vein. The patient exercised on a treadmill according to the Bruce procedure (Bruce, 1971) until he reached his maximal heart rate or developed chest pain or fatigue. Thallium, 2 mCi, was then injected, and the exercise was continued for an additional 60 seconds. The electrocardiogram was continuously monitored throughout the exercise study and during the imaging procedure which was performed in an adjacent room. Imaging began 10 minutes after injection. Rest myocardial images were obtained in two ways: (1) 29 patients were imaged one week before the exercise imaging procedure. Thallium, 2 mCi, was injected intravenously with the patient erect after fasting for 12 hours in order to minimise gastric and hepatic activity. Imaging began 10 minutes after injection; (2) 17 patients were re-imaged 4 hours after the exercise study according to the method of Pohost *et al.* (1977). Images were recorded in the anterior and 45 degree left anterior oblique position by rotating the detector with the patient supine, and in the left lateral position with the patient on his left side over the detector. Five hundred thousand counts were recorded in each position. An Elscint Model CE-1 scintillation camera (37 photomultiplier tube, 30 cm crystal diameter) equipped with a high resolution parallel hole collimator was used for all studies. Images were recorded with a 20 per cent window centred on 75 keV. Images were recorded on Polaroid film from the camera console and also digitised on line on magnetic disc as 128 × 128 static byte matrix pictures on a PDP[1] 11/45 computer running the GAMMA 11[1] nuclear medicine software. Polaroid pictures from the analogue data were flood corrected at the camera console during data collection using a built-in camera feature. Flood correction was performed by software on all computer images after data collection.

All studies were interpreted by two observers who had no knowledge of the angiographic or electrocardiographic findings. Five segments of the left ventricle (septal, anterolateral, posterolateral, inferior, and apical) were analysed using both the Polaroid (unprocessed) data and the computer processed data. Polaroid data were interpreted qualitatively according to the following criteria. Resting images were categorised as (a) normal if there was homogeneous tracer distribution of tracer uptake; or (b) abnormal if there was a focal reduction in tracer uptake in regions which normally have homogeneous distribution of radioactivity. The exercise study was considered positive if a new perfusion defect developed or if there was an increase in the rest defect.

The computer-processed images were displayed in 128 × 128 matrix and activity from equal regions of interest determined from the 5 segments of the left ventricle defined above. A significant perfusion defect was considered present at rest when there was a reduction of 20 per cent or greater in counts between one or more of the anatomical segments of the left ventricle (Strauss and Pitt, 1977). The exercise image was considered positive for ischaemia if a new perfusion defect as defined above appeared after exercise or if there was an increase in a defect also observed in the scintigrams obtained at rest.

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[1] Digital Equipment Corporation.

EXERCISE ELECTROCARDIOGRAPHY

Exercise electrocardiography was performed twice in each patient, initially during the clinical evaluation and again for exercise imaging. Standard graded treadmill exercise using the Bruce procedure (Bruce, 1971) was performed until the patient attained his maximal heart rate or developed angina pectoris or severe fatigue. The Frank lead system (Frank, 1956) and praecordial leads V4-6 were employed for monitoring before, during, and for 10 minutes after exercise. The treadmill exercise electrocardiogram was interpreted as positive if 1 mm or greater horizontal or downsloping ST segment depression of duration 0·08 s or more appeared during or immediately after exercise.

CORONARY ARTERIOGRAPHY

Coronary arteriography was performed using the Judkins technique in multiple projections on 35 mm film with a 4½ inch mode General Electric image intensifier. Coronary arteriograms were evaluated by an independent observer unaware of the myocardial perfusion image results. The percentage luminal narrowing of each angiographic lesion was measured and the location noted. Stenosis of greater than 70 per cent of one or more of three major coronary arteries was considered haemodynamically significant. Left ventriculography was performed in the right anterior oblique projection in all patients. Results were analysed statistically using the binomial test (Siegel, 1956).

Results

The results of the clinical data, resting and exercise electrocardiograms, thallium-201 myocardial perfusion scintigrams at rest and exercise, coronary arteriography, and left ventriculography are summarised in Table 1 for the patients with 70 per cent or greater coronary stenosis.

MYOCARDIAL PERFUSION SCAN INTERPRETATION

There was complete interobserver agreement in 38 of the 46 cases (84%) using the Polaroid images. Consensus was achieved in the remaining 8 cases using the computer processed data. In 3 of the 38 cases the Polaroid data were considered normal at rest by both observers, while a clinically confirmed defect was shown using the computer processed data.

ANGIOGRAPHY

Twenty-six of the patients had greater than 70 per cent stenosis of at least 1 of the 3 major coronary arteries. Six had single vessel disease, 11 had two vessel disease, and 9 patients had triple vessel disease. The remaining 20 patients had either normal coronary arteriograms or less than 50 per cent stenosis of a major coronary artery. No patient had lesions between 50 and 70 per cent stenosis

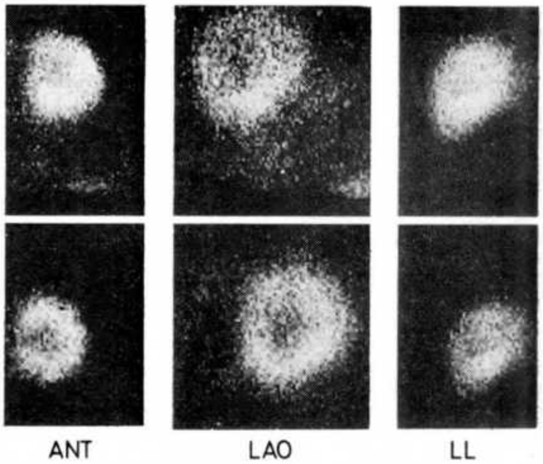

Fig. 1 *Normal thallium-201 myocardial perfusion scintigram at rest (upper panels) and exercise (lower panels) in a patient with normal coronary arteries on selective coronary arteriography.*
ANT, anterior view; LAO, left anterior oblique view; LL, left lateral view.

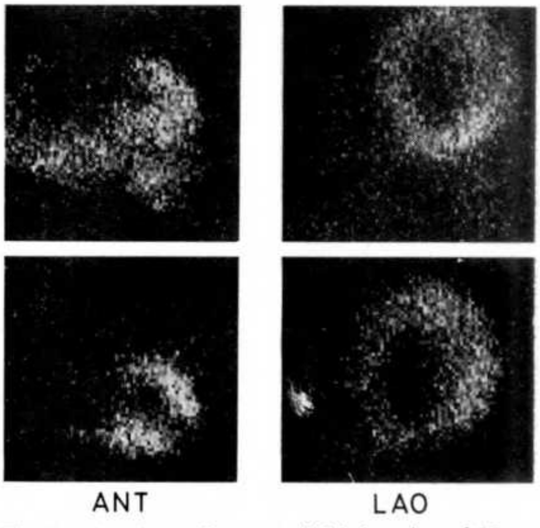

Fig. 2 *A patient with myocardial ischaemia and 95 per cent stenosis of the left anterior descending coronary artery. The thallium-201 scintigram is normal at rest (upper panels). After exercise there is a perfusion defect involving the apex and lower portion of the septum (lower panels).*

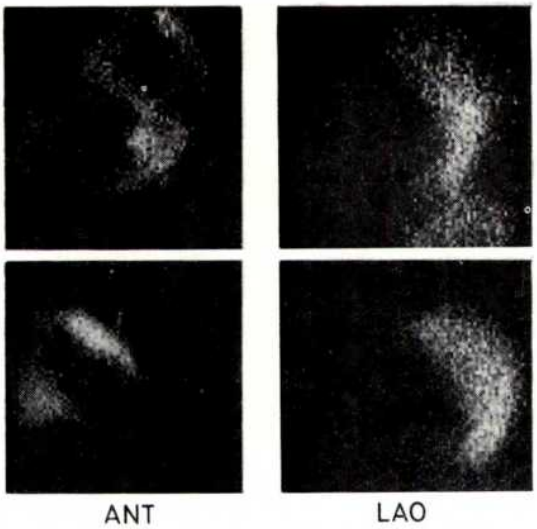

Fig. 3 *Thallium-201 myocardial perfusion scintigram in a patient with 100 per cent obstruction of the left anterior descending and right coronary arteries. There are focal defects involving the septum, apex and inferior walls of the left ventricle at rest (upper panels) which are unchanged after exercise (lower panels), consistent with myocardial infarction without ischaemia.*

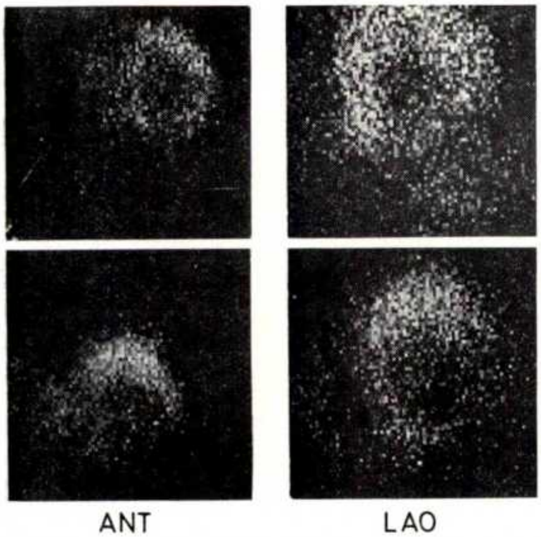

Fig. 4 *A patient with triple vessel coronary disease and a previous myocardial infarction. On the rest injected thallium scintigram (upper panel), there is decreased tracer concentration in the interior wall seen best in the LAO view. With injection at peak exercise (lower panel) the inferior defect becomes more obvious and there is decreased perfusion of the apex (ANT view), septum, and posterolateral walls (LAO view), consistent with myocardial infarction and ischaemia.*

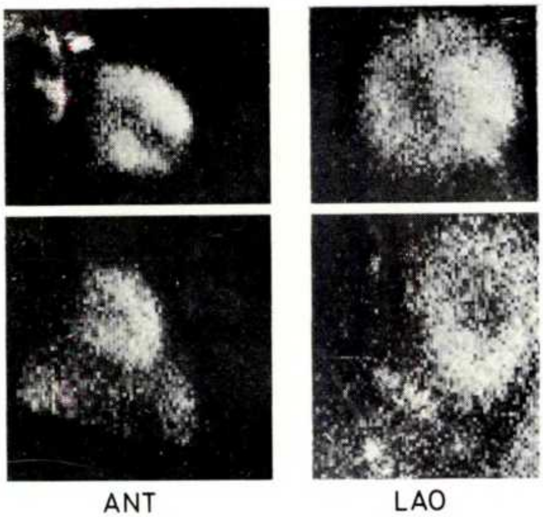

Fig. 5 *Thallium-201 myocardial perfusion scintigram 10 minutes after exercise (upper panel) and 4 hours later (lower panel). The decreased tracer concentration 10 minutes after exercise is not present 4 hours later, indicative of myocardial ischaemia. Coronary arteriography revealed 90 per cent obstruction of the left anterior descending coronary artery.*

without at least 1 major coronary artery narrowed more than 70 per cent.

PATTERNS OF THALLIUM-201 SCINTIGRAMS

Rest and exercise thallium-201 scintigrams in each patient were compared and classified as follows: (1) normal rest and normal exercise (Fig. 1); (2) normal rest and abnormal exercise, indicative of myocardial ischaemia (Fig. 2); (3) abnormal rest with no change on exercise, consistent with myocardial infarction without ischaemia (Fig. 3); (4) abnormal rest and abnormal exercise, consistent with myocardial infarction and ischaemia (Fig. 4). Scintigrams obtained 4 hours after exercise were similar to those obtained at a separate rest study 1 week before exercise. Exercise induced perfusion defects were not present in the scintigram 4 hours later in patients with myocardial ischaemia without infarction (Fig. 5).

ELECTROCARDIOGRAPHY AND PERFUSION SCINTIGRAPHY

The results of the rest and exercise electrocardiograms and the rest and exercise thallium-201 scintigrams are shown in Tables 1 and 2.

Resting thallium defects were present in 16 patients (62%) with significant coronary artery stenosis, while pathological Q waves were recorded

Table 1 *Data in patients with coronary stenosis*

Case no.	*Age*	*Sex*	*Clinical*		*ECG*		^{201}*Tl*		*Coronary angio % stenosis*			*LV angio wall motion*
			MI	*Angina (NYHA class)*	*Q*	*ETT*	*R*	*E*	*LAD*	C_x	*RCA*	
1	44	M	+	III	I	–	I	I	—	50	100	+2I
2	54	M	–	III	–	+	–	S, PL	90	70	60	0
3	60	M	+	II	–	+	I	I, S, PL	70	100	100	0
4	44	M	+	III	I, AS	+	I, S	I, S, PL	100	100	80	+1Ap
5	60	M	+	III	–	+	I, S	–	100	—	100	0
6	63	M	+	III	I	+	I, PL	I, PL, S	80	95	80	+1I
7	48	M	–	III	–	–	–	S	100	40	—	0
8	55	M	+	II	AS	–	S, I	–	100	80	50	+2Ap
9	56	M	+	III	A, L	–	S, PL	–	100	60	40	+3Ap
10	60	M	–	III	–	–	–	I, S, PL	95	60	—	0
11	61	M	+	IV	I	–	I	I, S	100	95	100	+2I
12	63	F	+	IV	I	+	I	I, S, PL	100	90	90	0
13	72	M	+	II	AS	+	–	I, S, PL	100	90	100	0
14	60	M	–	II	–	+	—	I, S, PL	95	95	70	0
15	67	M	+	III	AS	–	S	S, I, PL	100	100	—	+1A
16	55	M	–	III	–	+	—	S, I	100	40	60	0
17	74	M	+	III	I	+	I	I, S	90	—	100	+2I
18	60	F	–	III	–	+	—	—	90	—	80	0
19	53	M	+	III	I, AS	+	I, S	I, S, Ap	90	100	80	+2Ap
20	69	M	+	IV	AS	+	S	S, PL, I	100	70	60	0
21	49	M	+	III	–	+	S	S, I	100	90	30	0
22	52	M	–	II	–	–	—	I, PL	100	100	90	0
23	58	M	+	II	S	–	S	S, I	100	—	90	+2Ap
24	65	M	+	III	–	+	I, PL	—	50	100	100	+1I
25	57	M	–	III	–	–	—	S	90	—	—	0
26	63	F	–	II	–	–	—	S, I	95	—	80	0

Abbreviations: MI = myocardial infarction; NYHA = New York Heart Association Functional classification; ECG = electrocardiogram; Q = Q wave $\geqslant$ 0·04 s; ETT, exercise tolerance test; ^{201}Tl, thallium myocardial perfusion scintigram; R, rest; E, exercise; LAD, left anterior descending coronary artery; C_x, circumflex coronary artery; RCA, right coronary artery; wall motion: o, normal; +1, hypokinesis; +2, akinesis; +3, dyskinesis; A, anterior; AS, anteroseptal; I, inferior; S, septum; L, lateral; PL, posterolateral; Ap, apex; +, present or abnormal –, absent or negative.

in 13 patients (50%). Myocardial perfusion defects in the resting scintigram correlated very well with evidence of previous myocardial infarction (16 of 17 patients, 94%); significant Q waves were present in 13 of these 17 patients (76%). Of the 17 patients with documented past evidence of infarction but without significant Q waves in current electrocardiograms, 3 had localised perfusion defects at rest. Of the 16 patients with rest thallium-201 defects, 11 had asynergy whereas of the 13 patients with Q waves, 10 had asynergy.

The proportion of patients with a positive exercise thallium-201 scintigram (21 of 26 patients, 81%) was greater than the proportion with a positive

Table 2 *Results of electrocardiogram and thallium-201 myocardial imaging interpretation in 26 patients with > 70 per cent coronary stenosis*

	No.	*Per cent*
Rest		
Q > 0·04 second	13	50
Scintigram abnormal	16	62
Q > 0·04 second/abnormal scintigram	17	65
Exercise		
Exercise ECG abnormal	15	58*†
Scintigram abnormal	21	81*
Exercise ECG abnormal/scintigram abnormal	23	88†
Combined		
Q > 0·04 second or exercise electrocardiogram abnormal	21	81
Rest or exercise scintigram abnormal	25	96

* P < 0·05 abnormal scintigram compared with abnormal exercise electrocardiogram.

† P < 0·01 abnormal exercise electrocardiogram/abnormal scintigram compared with abnormal exercise electrocardiogram.

Table 3 *Sensitivity and specificity of thallium exercise scintigraphy and exercise electrocardiography*

	Coronary arteriography Coronary stenosis	
	Significant stenosis (> 70%)	*No significant stenosis (< 50%)*
Exercise scintigram		
Abnormal	21	2
Normal	5	18
Total	26	20
	Sensitivity 81%*	Specificity 90%†
Exercise electrocardiogram		
Abnormal	15	7
Normal	11	13
Total	26	20
	Sensitivity 58%*	Specificity 65%†

* P < 0·05—sensitivity exercise scintigram compared with exercise electrocardiography.

† P < 0·05—specificity exercise scintigram compared with exercise electrocardiography.

Table 4 *Results of electrocardiogram and thallium-201 imaging related to number of coronary vessels with > 70 per cent stenosis*

Coronary vessels involved	*No.*	*Abnormal electrocardiogram*			*Abnormal thallium-201 scintigram*		
		Q	*Exercise ECG*	*Q wave or exercise ECG*	*Rest*	*Exercise*	*Rest or exercise*
1	6	2	1	3	2	4	6
2	11	6	6	9	8	8	10
3	9	5	8	9	6	9	9

Abbreviations: Q, Q wave 0·04 s or longer; ECG, electrocardiogram.

exercise electrocardiogram (15 of 26 patients, 58%, $P < 0\cdot05$). The sensitivity for the detection of ischaemia was increased when the results of the two procedures at exercise were combined (23 of 26 patients, 88%), being significantly greater than with the exercise electrocardiogram alone ($P < 0\cdot01$).

Of the 26 patients with coronary stenosis greater than 70 per cent, significant Q waves at rest and/or a positive exercise electrocardiogram were present in 21 (81%). Abnormal rest and/or exercise thallium-201 perfusion defects were present in 25 of the 26 patients (96%). The results were unchanged when coronary stenosis greater than 50 per cent was classed as significant.

Each of the 20 patients with normal coronary arteriograms had normal thallium-201 myocardial perfusion scintigrams at rest. Two of the 20 patients with normal rest scintigrams developed perfusion defects on exercise associated with chest pain and positive exercise electrocardiograms. Five additional patients with normal rest and exercise thallium-201 scintigrams had positive exercise electrocardiograms. No patient had significant Q waves. The specificity and sensitivity of exercise thallium scintigrams and exercise electrocardiograms are shown in Table 3.

The sensitivity of thallium-201 myocardial perfusion scintigraphy and electrocardiography related to the number of coronary arteries with greater than 70 per cent stenosis is shown in Table 4. While each of the patients with triple vessel disease had positive exercise perfusion scintigrams and positive exercise electrocardiograms, the thallium-201 (rest or exercise) scintigram was more sensitive than the rest or exercise electrocardiogram in patients with single vessel disease (6 of 6 patients vs. 3 of 6 patients). There was a progressive increase in both positive exercise scintigrams and exercise electrocardiograms with the number of coronary arteries involved.

Table 5 *Correlation of thallium-201 scintigraphy and arteriography*

Coronary artery % Stenosis	*No. of cases*	*Abnormal thallium-201*
LAD		
⩾ 50%	25	22
⩾ 70%	24	22
Cx		
⩾ 50%	18	13
⩾ 70%	15	11
RCA		
⩾ 50%	20	18
⩾ 70%	16	15

LAD, left anterior descending coronary artery; Cx, circumflex coronary artery; RCA, right coronary artery; abnormal thallium-201, abnormal rest or exercise thallium perfusion scintigrams.

The correlation of perfusion defects on the rest or exercise thallium-201 study with the anatomical location of coronary artery stenosis greater than 70 per cent is presented in Table 5. Anterior, apical, or septal perfusion defects were present in 22 of the 24 patients with left anterior descending disease, inferior defects in 15 of the 16 patients with right coronary disease, and posterolateral defects in 11 of the 15 patients with circumflex disease. The correlation is similar when coronary stenosis greater than 50 per cent is considered significant.

Discussion

DETERMINANTS OF THALLIUM MYOCARDIAL DISTRIBUTION

The initial distribution of thallium-201 in the myocardium is dependent on both coronary blood flow and cellular extraction (Strauss *et al.*, 1975; Strauss and Pitt, 1977). Strauss *et al.* (1975) compared the regional myocardial distribution of thallium-201 with that of radioactive microspheres under conditions of normal flow, and partial and complete coronary occlusion; the data indicate that the major determinant of thallium-201 distribution is blood flow. The results of studies of extraction efficiency under various experimental conditions are conflicting (Costin and Zaret, 1976; Weich *et al.*, 1977). Image defects in the rest thallium-201 scintigram generally represent myocardial infarction (Hamilton *et al.*, 1977). In the resting non-ischaemic state, viable myocardial regions supplied by stenotic coronary arteries are usually adequately perfused in either an anterograde or retrograde fashion. Resting coronary blood flow and regional distribution were both normal in animals, despite coronary stenosis of 85 per cent in diameter (Gould *et al.*, 1974). However, the ability to increase coronary flow in response to stress became progressively abnormal with coronary stenosis exceeding 45 per cent. In the present study, normal thallium-201 rest images were found in patients with 90 to 95 per cent coronary stenosis, unless prior infarction had occurred. Under stress, myocardial segments supplied by coronary arteries with 50 per cent or greater luminal narrowing became transiently ischaemic resulting in a perfusion defect that correlated well with the specific coronary artery which was stenosed.

SENSITIVITY AND SPECIFICITY OF PERFUSION SCINTIGRAPHY AND ELECTROCARDIOGRAPHY

Significant coronary artery stenosis may result in myocardial infarction, in myocardial ischaemia, or it may be silent. Therefore, the demonstration of infarction and/or ischaemia is considered evidence of significant coronary stenosis. Both abnormal Q waves in the resting electrocardiogram and exercise induced ST segment depression lack specificity and sensitivity (Horan *et al.*, 1971; Borer *et al.*, 1975; Fortuin and Weiss, 1977). The results of the present study show that the sensitivity of exercise induced scintigraphic abnormalities (81%) is higher than ST segment depression (58%) on the exercise electrocardiogram ($P < 0{\cdot}05$), confirming recent studies evaluating these procedures in patients with myocardial ischaemia (Bailey *et al.*, 1977; Ritchie *et al.*, 1977a, b; Botvinick *et al.*, 1978). Combined exercise thallium-201 scintigraphic and electrocardiographic evaluation was more sensitive than the exercise electrocardiogram alone ($P < 0{\cdot}01$). Therefore the two procedures are complementary. Rest and exercise thallium-201 scintigraphy seem more sensitive in the detection of haemodynamically significant coronary artery disease than rest and exercise electrocardiography but because of the small number of patients studied this was not statistically significant ($0{\cdot}01 > P > 0{\cdot}05$). The specificity of thallium-201 exercise scintigraphy in this study was 90 per cent while the specificity of exercise electrocardiography was 65 per cent ($P < 0{\cdot}05$). These results, similar to those of Ritchie *et al.* (1977a) and Botvinick *et al.* (1978), were obtained from a selected population; more experience is necessary before the specificity of thallium scintigraphy is definitely established.

FALSE NEGATIVE EXERCISE THALLIUM SCINTIGRAMS

Five patients with significant coronary stenosis exercised to the development of angina pectoris had false negative exercise thallium-201 scintigrams. Four had an old extensive myocardial infarction documented by Q waves 0·04 s or greater and an abnormal rest thallium-201 image. The absence of an increase in the rest image defect with exercise may be the result of the infarct concealing an adjacent region of exercise-induced ischaemia. The exercise electrocardiogram was negative in 3 of these 4 patients. While previous studies have suggested that in patients with severe triple vessel disease, global ischaemia may be produced by exercise and a focal perfusion defect may not appear (Pitt and Strauss, 1976), it is noteworthy that each of our patients with angiographically significant triple vessel disease had positive exercise thallium-201 scintigrams. Two of the 5 patients with false negative exercise scintigrams had single vessel disease and 3 had double vessel disease. It is important to remember that the coronary arteriogram reflects an anatomical state, whereas the myocardial perfusion scan reflects the functional regional status of myocardial perfusion. A direct relation between the two techniques does not always exist. Furthermore, the appearance of chest pain during exercise in the absence of ST segment depression and/or a myocardial perfusion defect does not indicate that the patients were in fact ischaemic and, therefore, that the above tests were true false negatives.

SCINTIGRAPHY AND CORONARY ARTERIOGRAPHY

The correlation of thallium perfusion defects at rest and/or exercise with angiographically significant coronary stenosis was higher for the left anterior descending and right coronary arteries than for the circumflex coronary artery. These results are similar to those reported by McLaughlin *et al.* (1977) though the correlation in the present study was slightly higher for circumflex artery disease.

ADVANTAGES OF 4-HOUR POST-EXERCISE STUDY

Our results with patients imaged 10 minutes after exercise and 4 hours later agree with those of Pohost *et al.* (1977) and Blood *et al.* (1977). Exercise induced perfusion defects were not apparent after 4 hours in patients with coronary stenosis without infarction. The images obtained 4 hours after exercise were similar to rest images obtained 1 week before the exercise study. This confirms that 2 separate studies 1 week apart are not necessary. In addition to the information being available the same day, the exercise and 4-hour post-exercise study technique requires only 1 dose of thallium-201 and, therefore, is less expensive and provides less radiation exposure.

CLINICAL IMPLICATIONS

Myocardial perfusion scintigraphy with thallium-201 is a safe, non-invasive diagnostic technique. The images are of good quality, and can be obtained with a conventional gamma scintillation camera. Thallium-201 scintigraphy represents an objective screening test for identifying significant coronary artery disease in patients with an atypical clinical history and a negative exercise electrocardiogram, and for confirming suspected myocardial infarction. This technique is helpful in assessing the presence or absence of coronary disease in asymptomatic patients with a positive exercise electrocardiogram (Zaret *et al.*, 1973a; Caralis *et al.*, 1977), and for evaluating the results of aortocoronary bypass surgery (Greenberg *et al.*, 1977; Kostuk *et al.*, 1977; Narahara *et al.*, 1977; Ormand *et al.*, 1977; Sbarbaro *et al.*, 1977; Wainwright *et al.*, 1977; Corne *et al.*, 1979), pharmacological interventions (Salel *et al.*, 1974), and modifications of risk factors for coronary artery disease. More experience with this technique is necessary before the specificity is established. We have found that the quantitative computer method employed in this study was of value in those cases of interobserver disagreement using non-processed analogue images and also increased the sensitivity in the interpretation of rest scintigrams. It is anticipated that when comparative studies of medical and surgical treatment are evaluated a more accurate estimate of regional myocardial perfusion will be available than with visual analysis of analogue images.

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Effects of oxygen administration, bicarbonate infusions, and brief hyperventilation on patients with pulmonary vascular obstructive disease

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SUMMARY In an attempt to clarify further the mechanisms underlying labile rise in pulmonary vascular resistance, the effects of administering high oxygen concentrations, brief voluntary hyperventilation, and correction of acidosis were studied in 16 patients in whom congenital heart disease was associated with pulmonary vascular disease. On breathing 100 per cent oxygen there was a significant fall in pulmonary vascular resistance from 21·8 ± 4·6 to 12·9 ± 3·6 units/m^2 ($P < 0·001$), with a rise in pulmonary blood flow from 4·4 ± 0·6 to 8·8 ± 2·0 l/min per m^2 ($P < 0·025$) and a fall in pulmonary artery pressure from 67·8 ± 2·8 to 61·8 ± 4·0 mmHg ($P < 0·025$). The changes occurring on sodium bicarbonate administration in 6 patients did not reach levels of significance, but the size of each individual response was closely correlated with the response to oxygen administration. No significant changes occurred either on voluntary hyperventilation or, in the systemic circulation, with any intervention. However, systemic vascular resistance was positively correlated with pulmonary vascular resistance ($P < 0·01$). As a result of this, though age was correlated positively with both pulmonary artery mean pressure ($P < 0·025$) and vascular resistance ($P < 0·025$), it was not correlated with the ratio of pulmonary to systemic resistance. Since pulmonary vascular disease is progressive, these results cast some doubt on the validity of resistance ratio as a measure of its severity.

Patients with congenital heart disease, particularly when this involves communications between the pulmonary and systemic circulations at ventricular or great arterial level, or concordant (complete) transposition of the great arteries, are at risk of developing pulmonary vascular obstructive disease. This in turn is a major determinant of both immediate and late surgical mortality for correction of the defect (Blount and Woodwark, 1960; Goodwin, 1961; Kirklin, 1965; Cartmill *et al.*, 1966; Mair *et al.*, 1974, 1976). The degree of pulmonary vascular obstructive disease can be assessed directly before attempted correction by lung biopsy (Heath *et al.*, 1958b), though this has distinct limitations (Adams *et al.*, 1957; Wagenvoort *et al.*, 1967). A promising, but as yet untested, new technique is inhalation and injection of radioactive nitrogen (^{13}N) (McKenzie *et al.*, 1977). However, the most widely used and tested method is that of assessing pulmonary vascular resistance (or derivatives thereof) during cardiac catheterisation (Adams *et al.*, 1957; Blount and Woodwark, 1960; Goodwin, 1961; Kirklin and DuShane, 1963; Hallman *et al.*, 1964; Kirklin, 1965; Cartmill *et al.*, 1966; Kimball and McIlroy, 1966; Reeve *et al.*, 1966; Hallidie-Smith, 1968; Gotsman *et al.*, 1969; Mair *et al.*, 1974, 1976). A major limitation of this method is that the sedation required to catheterise children itself affects pulmonary vascular resistance (Auld *et al.*, 1963), and may thereby cause pulmonary vascular disease to appear far more severe when assessed by cardiac catheterisation than when judged by clinical examination in the unsedated patient (Hallidie-Smith *et al.*, 1969). Apart from the direct effects of the drug used for sedation, the most likely causes of an artefactual rise in pulmonary vascular resistance during catheterisation are pulmonary venous hypoxia (caused either by hypoventilation or by atelectasis) and acidaemia. Accordingly we set out to study prospectively the effects of (a) administra-

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tion of high oxygen concentrations, (b) voluntary hyperventilation, and (c) sodium bicarbonate administration on the haemodynamics of patients with pulmonary vascular obstructive disease.

Methods

The subjects were patients with congenital heart disease in whom the pulmonary vascular resistance was known to be, or strongly suspected to be, raised to levels which might increase the risks and morbidity of surgery or even make surgical intervention prohibited. Patients with obstruction of any type of pulmonary venous return were excluded.

All patients were studied in the fasting state, lightly sedated after being premedicated either with 0·025 ml/kg of a mixture containing phenoperidine 0·025 mg/ml and dehydrobenzperidol 2·5 mg/ml, or with 0·1 ml/kg of a mixture containing pethidine 25 mg/ml, promethazine hydrochloride 6·25 mg/ml, and chlorpromazine 6·25 mg/ml (maximal dose 3 ml). Cardiac catheterisation was performed under local anaesthetic (lignocaine HCl 1%). Whenever practicable separate cardiac catheters were passed to the main pulmonary artery (both branches in the presence of a persistent ductus arteriosus), the right atrium (also for superior and inferior vena cava blood sampling), left atrium (and one or more pulmonary veins), and a systemic artery. In a few cases, rapid sequential sampling from all these sites was used. Thus, blood sampling for oxygen saturation and pressure recordings were performed simultaneously, or nearly so, together with the measurement of oxygen consumption by the flow-through method (Kappagoda *et al.*, 1973).

Haemodynamic data were first obtained at rest, breathing room air normally. In 6 subjects significant metabolic acidosis, as indicated by the non-respiratory $pH < 7{\cdot}31$ (Kappagoda *et al.*, 1970, 1972), was present and measurement of all haemodynamic data was repeated, including measurement of oxygen consumption, after this acidosis had been corrected. This was done by giving 8·4 per cent w/v sodium bicarbonate at a constant rate of 2 mmol/min, by infusion pump, until the acidosis, as measured in repeated blood samples, was corrected.

Four subjects were then asked to hyperventilate for one minute, after which time all haemodynamic measurements were repeated, including measurement of the oxygen consumption. Most children found voluntary hyperventilation impossible.

Finally 100 per cent oxygen was administered by close-fitting face mask for 10 minutes to all subjects and haemodynamic measurements were repeated. Oxygen consumption was not remeasured during oxygen administration but was assumed to have remained unchanged (Barratt-Boyes and Wood, 1958).

The pulmonary and systemic flows were calculated using the Fick method. In the presence of a left-to-right shunt mixed venous (MV) oxygen saturation was obtained from the superior and inferior vena cava (SVC and IVC) saturations (Flamm *et al.*, 1969; Miller *et al.*, 1974):

$$\mathrm{MV} = \frac{(3 \times \mathrm{SVC}) + (1 \times \mathrm{IVC})}{4}.$$

In the 3 patients with associated persistent ductus arteriosus and 2 patients with persistent truncus the mixed pulmonary arterial sample was taken as the mean of both pulmonary arteries. Arterial blood gases were taken from each site, and dissolved oxygen in the plasma was calculated as 0·3 ml/100 ml per 100 mmHg (Slonim *et al.*, 1967).

In all cases the pulmonary venous blood was obtained directly from the left atrium or pulmonary veins, if necessary by retrograde left atrial catheterisation (Morrison *et al.*, 1977). No assumptions were, therefore, made about the pulmonary venous oxygen saturation or the mean left atrial pressure. Similarly no assumptions were made for oxygen consumption. Pulmonary and systemic resistances were obtained from the pressure gradients and flows across the respective vascular beds.

In order to determine whether there were specific disturbances in systemic vascular resistance related to pulmonary vascular disease, the actual values of systemic vascular resistance were compared with those predicted from a study of 150 unselected patients with congenital heart disease (Morrison and Macartney, 1978). The factors taken into account in making this prediction were premedication, body size, haematocrit, and systemic arterial oxygen saturation.

Comparisons of haemodynamic data under varying ambient conditions were made using the paired Student's t test. Correlations were investigated by linear regression analysis.

Results

Out of 1300 cardiac catheterisations performed during the past 5 years investigation of the lability of raised pulmonary resistance was carried out in 16 subjects (1·2%). The median age of subjects was 8·9 years (range 0·7-37 years) and the median weight was 30·6 kg (range 5·6 to 42 kg). The mean haematocrit was 41·2 per cent (range 34 to 60%), and the mean systemic oxygen saturation breathing

Table *Anatomical diagnosis and outcome in patients investigated*

Case no.	*Basic diagnosis*	*Pulmonary vascular resistance (units/m²)*		*Outcome*
		Air	O_2	
1	Double outlet right ventricle	38	22	Died after 33 months
2	Ligated persistent ductus arteriosus	23	14	Alive after 28 months
3	Ventricular septal defect	8·2	8·3	Alive after 32 months
4	Ventricular septal defect; persistent ductus arteriosus	13	4·2	Alive after 63 months
5	Concordant transposition of great arteries; ventricular septal defect	8·9	3·6	Died postoperatively
6	Persistent truncus arteriosus	71	55	Died after 1 month
7	Ventricular septal defect; persistent ductus arteriosus	11·5	6·6	Alive after 40 months
8	Ventricular septal defect; persistent ductus arteriosus	14	2·7	Alive after 45 months
9	Ventricular septal defect	15	7·4	Alive after 53 months
10	Common atrioventricular orifice	22	8·8	Alive after 49 months
11	Common atrioventricular orifice	46	23	Alive after 48 months
12	Concordant transposition of great arteries; ventricular septal defect	9·5	5·0	Died postoperatively
13	Persistent truncus arteriosus	12	3·9	Died 1 month postoperatively
14	Ventricular septal defect	7·0	5·6	Surgical correction; alive after 55 months*
15	Common atrioventricular orifice	5·5	1·7	Died postoperatively*
16	Primitive ventricle	44	35	Alive after 59 months

*Pulmonary artery mean pressure fell to 50 per cent of systemic mean pressure.

room air was 79·9 per cent (range 56 to 97%). The basic diagnoses of these 16 cases are shown in the Table.

(I) CONTROL HAEMODYNAMIC DATA

Age had a significant positive correlation with mean pulmonary artery pressure ($P < 0{\cdot}025$) and a negative correlation with pulmonary blood flow ($P < 0{\cdot}01$). Both these factors are involved in the calculation of pulmonary vascular resistance and there was a significant positive correlation of pulmonary vascular resistance with age ($P < 0{\cdot}01$) (Fig. 1). Pulmonary vascular resistance (PVR) had a significant positive correlation with systemic vascular resistance (SVR) ($P < 0{\cdot}01$) (Fig. 2). There was no significant correlation between age and the ratio PVR/SVR (Fig. 3). Nor was there any correlation between mean left atrial pressure and total pulmonary blood flow in l/min per m². When information on premedication, body size, haematocrit, and systemic oxygen saturation was fed into a previously derived equation (Morrison and Macartney, 1978) predictive of absolute systemic vascular resistance, the absolute measured value

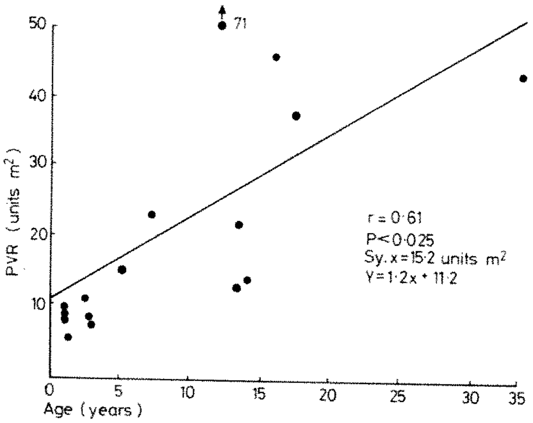

Fig. 1 *The relation of pulmonary vascular resistance to age.*

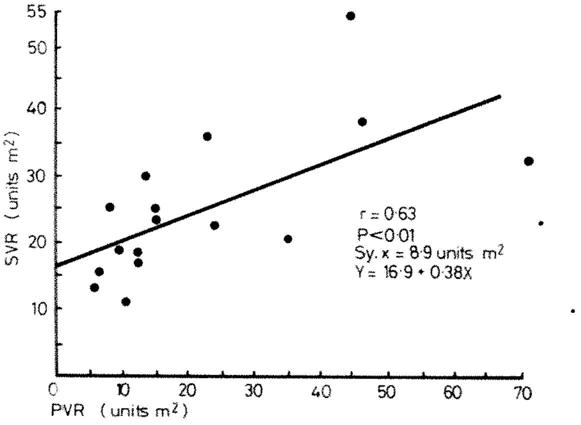

Fig. 2 *The relation between systemic and pulmonary vascular resistance.*

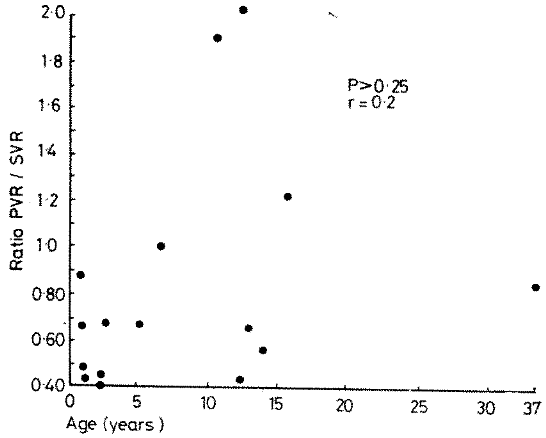

Fig. 3 *The relation between the vascular resistance ratio and age.*

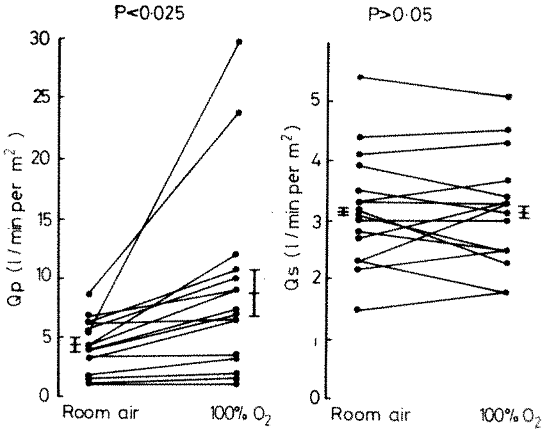

Fig. 5 *The response of pulmonary and systemic blood flows to breathing oxygen. The bars represent the means and their standard errors.*

of 32·7 ± 2·0 units (±SEM) was slightly lower than the predicted value of 34·5 ± 2·4 units, but this difference was not statistically significant.

(II) EFFECTS OF BREATHING 100 PER CENT OXYGEN

On breathing 100 per cent oxygen there was a fall in pulmonary artery mean pressure in all except 3 out of the 16 patients, and the overall decrease was highly significant ($P < 0{\cdot}025$). Those 3 patients who had a rise in mean pulmonary artery pressure were among the 5 with the highest control pressures (Fig. 4). There was a rise in pulmonary artery blood flow in all of the 16 patients ($P < 0{\cdot}025$) (Fig. 5). With a fall in pressure and an increase in flow, the calculated pulmonary vascular resistance fell in all except 1 case, and this result is highly significant ($P < 0{\cdot}001$) (Fig. 6). There was no significant change in left atrial pressure during oxygen administration. Pulmonary venous P_{O_2} rose to a mean of 332·6 mmHg. There was considerable individual variation, however, the range being 200 mmHg to 467 mmHg.

The numerical change in pulmonary vascular resistance was closely correlated with the magnitude of the original pulmonary vascular resistance in air ($P < 0{\cdot}01$) (Fig. 7).

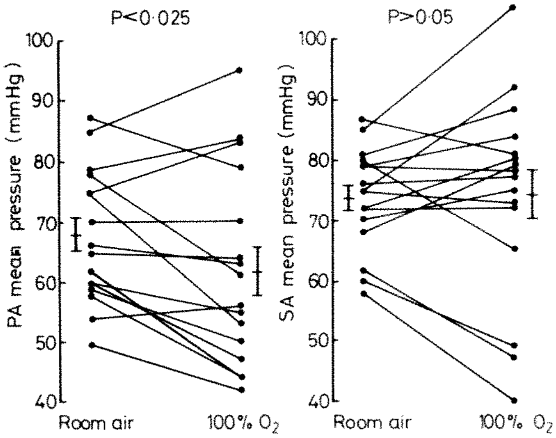

Fig. 4 *The response of the mean pulmonary and systemic arterial pressures to oxygen. The bars show means and their standard errors.*

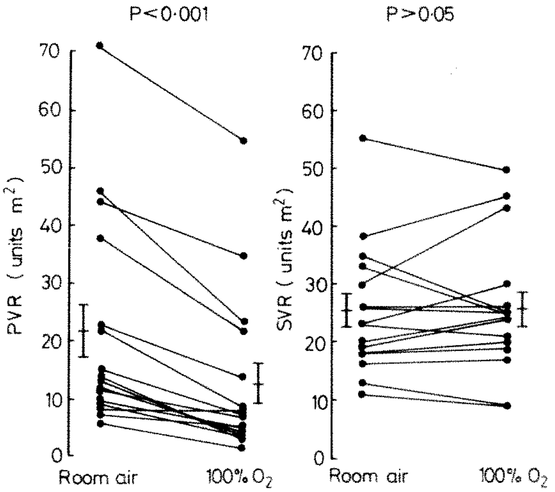

Fig. 6 *The response of the pulmonary and systemic vascular resistance to oxygen. The bars represent means and their standard errors.*

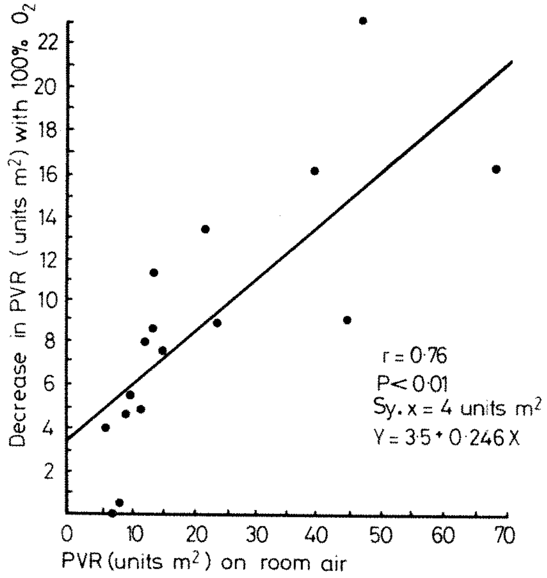

Fig. 7 *The relation between the decrease in pulmonary vascular resistance induced by breathing oxygen, and the original level of pulmonary vascular resistance.*

We have seen that systemic vascular resistance increased with increasing pulmonary vascular resistance in Section I of these results. On exposure to 100 per cent oxygen there was no significant change in the mean systemic arterial pressure (Fig. 4), systemic blood flow (Fig. 5), or systemic vascular resistance (Fig. 6). The most striking effect of breathing oxygen on the mean systemic arterial pressure was to widen the range of values found (Fig. 4). The response could not be correlated, in direction or magnitude, with the age of the patient, the resting systemic arterial oxygen saturation, or the resting pulmonary vascular resistance. Because pulmonary vascular resistance changed independently of systemic vascular resistance in 100 per cent oxygen, there was a significant decrease in the ratio PVR/SVR in 100 per cent oxygen (P < 0·001).

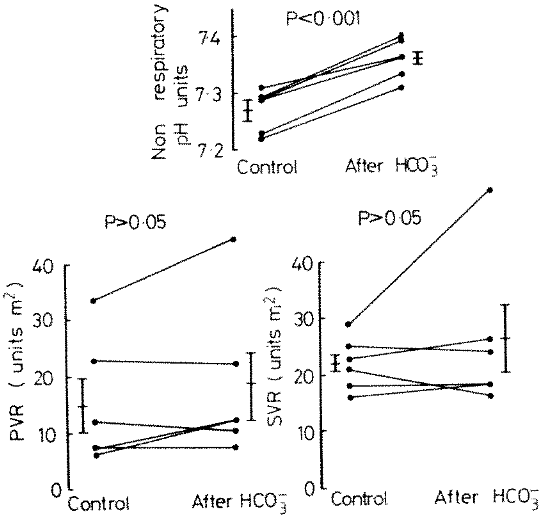

Fig. 8 *The response of pulmonary and systemic vascular resistances to correction of metabolic acidosis by means of intravenous infusion of sodium bicarbonate. The bars indicate means and their standard errors.*

(III) ADMINISTRATION OF BICARBONATE

The results in 6 subjects are reported (Fig. 8). The mean non-respiratory *p*H in these subjects was 7·26 initially, and 7·36 after administration of bicarbonate. This rise is statistically significant (P < 0·001). The mean requirement of bicarbonate was 1·8 mmol/kg (range 0·9 to 3·3 mmol/kg).

On administration of bicarbonate to correct metabolic acidosis there was no significant change in the mean pulmonary artery pressure, pulmonary blood flow, or pulmonary vascular resistance. Similarly, there was no statistically significant change in the mean systemic arterial pressure, blood flow, or resistance, and no change in the mean left atrial pressure. There was no correlation between change in pulmonary vascular resistance and the original pulmonary vascular resistance, ratio of PVR/SVR, or change in non-respiratory *p*H. There was no significant change in Pco_2 during bicarbonate infusion. One interesting result did emerge from the bicarbonate experiments.

When the changes in pulmonary vascular resistance experienced by the 6 subjects who had bicarbonate infusions were compared with the responses of the same 6 subjects during oxygen administration a positive linear correlation was observed (P < 0·05). This suggests that pulmonary arterioles which react to one stimulus are likely to react to others.

(IV) HYPERVENTILATION

The results of 4 subjects were observed. Little change in pulmonary vascular resistance was produced, and though systemic vascular resistance rose in 3 patients and remained static in the fourth, this change did not achieve statistical significance.

(V) FATE OF PATIENTS STUDIED

Surgery was attempted in 5 patients, in only 1 of whom was the outcome satisfactory. The details of these and the fate of the other patients are summarised in the Table.

Of the 10 patients considered to be inoperable, 8 remain alive after a mean follow-up time of 4 years. The 2 patients who died had severely raised pulmonary vascular resistance.

Discussion

EFFECT OF INTERVENTION ON PULMONARY VASCULAR BED

With the developments of cardiac surgery in the late 1950's and early 1960's it became apparent that there was a group of patients in whom the risks of surgery were high and in whom the results were poor. These patients were characterised by extreme elevation of the pulmonary resistance, and high right heart and pulmonary artery pressures, associated with only small left-to-right, bidirectional, or reversed cardiac shunts.

The importance of a rise in the pulmonary vascular resistance in congenital heart disease was recognised by Moschowitz in 1927. The classical situation was recognised in large interventricular septal defects, forming one aspect of the natural history of this cardiac anomaly (Fyler *et al.*, 1958; Wood, 1958; Clarkson *et al.*, 1968). A rise in the pulmonary vascular resistance is now well recognised as a potential complication of any large left-to-right cardiac shunt or concordant transposition of the great arteries.

Whereas severe increases in pulmonary vascular resistance are rare in atrial septal defect below the age of 20 years (Swan *et al.*, 1959) and rare in ventricular septal defect below the age of 2 years (Kidd *et al.*, 1965), they are common in patients with transposition of the great arteries even within the first year of life (Newfeld *et al.*, 1974; Lakier *et al.*, 1975; Clarkson *et al.*, 1976).

Ever since the studies of Harris (1956) and Wood *et al.* (1956) using acetylcholine it has been hoped that administration of oxygen or pulmonary vasodilators will distinguish between 'fixed' and 'reactive' pulmonary hypertension. Heath and Edwards (1958) proposed a histological classification of pulmonary vascular changes and related the severity of these to the reversibility of pulmonary hypertension after closure of atrial and ventricular septal defects (Heath *et al.*, 1958b). However, no convincing correlation between response to 100 per cent oxygen and histological changes has been established (Heath *et al.*, 1958a). In this study total pulmonary resistance tended to be higher in patients with grade 4 to 6 disease whether they were breathing room air or 100 per cent oxygen. Swan and colleagues (1959) reported that in patients undergoing closure of pulmonary hypertensive atrial septal defect, survival was much better if pulmonary vascular resistance breathing oxygen fell below 80 per cent of the resistance breathing room air. However, the ratio of total pulmonary to systemic resistance breathing room air predicted survival just as well, and no correlation between response to oxygen and histological changes in the pulmonary vessels could be established.

Though in 3 of our most severely pulmonary hypertensive patients, mean pulmonary artery pressure rose on administering oxygen, in the majority it fell. In every single patient, pulmonary blood flow rose, and pulmonary vascular resistance fell at least 20 per cent in every patient except one whose resistance on room air was relatively mildly raised at 8·2 units/m^2 and remained unchanged on 100 per cent oxygen. Thus, in our experience even severely raised pulmonary vascular resistance remains responsive to administration of oxygen. While it is true that others have reported patients in whom there was no apparent response to 100 per cent oxygen (Swan *et al.*, 1959; Marshall *et al.*, 1961; Krongrad *et al.*, 1973), it should be noted that the present study is the only one concerning shunts at ventricular or great arterial level in which the left atrial and pulmonary venous oxygen saturations and pressures were directly measured. The indirect left atrial pressure is particularly unreliable in the presence of pulmonary vascular disease (Shepherd and Wood, 1959). Furthermore, during breathing of 100 per cent oxygen, the quantity of dissolved oxygen in the plasma assumes great importance in calculation of pulmonary flow by the Fick method. We found, as have others (Eggers *et al.*, 1962), that pulmonary venous Po_2 and therefore plasma dissolved oxygen was variable while breathing 100 per cent oxygen in the manner described, and therefore wonder about the wisdom of assuming that plasma dissolved oxygen is constant (Marshall *et al.*, 1961; Krongrad *et al.*, 1973). We did assume that no changes in oxygen consumption occurred during breathing 100 per cent oxygen, as found by Barratt-Boyes and Wood (1958) in healthy subjects. Such small increases (3 to 5%) as were detected in patients with congential heart disease (Swan *et al.*, 1959; Marshall *et al.*, 1961) would only have served to accentuate the drop in pulmonary vascular resistance, had they been allowed for.

This fall in pulmonary vascular resistance took place without any significant change in left atrial pressure. To a considerable extent, the total fall was predictable from the control value breathing room air. The higher the control value the greater the fall on breathing 100 per cent oxygen. We conclude that testing these patients with 100 per cent oxygen provided only slightly more information about the state of the pulmonary vascular bed than did measuring pulmonary vascular resistance on room air. If patients exist who have severe pulmonary vascular disease which is completely unresponsive to breathing 100 per cent oxygen, it seems likely that the pulmonary vascular resistance while breathing room air would be so high as to rule out operation in any case.

Although acidosis is known to cause pulmonary arteriolar constriction (Bergofsky *et al.*, 1962) and is thought to contribute to pulmonary arteriolar obstruction in patients with pulmonary vascular disease (Rudolph, 1966), there have been no reports of the response of the pulmonary circulation to correction of acidosis in pulmonary vascular disease.

Similarly, there have been no reports of the effects of altered P_{CO_2} as produced by voluntary hyperventilation, on the pulmonary resistance, though a single report in 1960 (Fishman *et al.*) indicated that an increase in inspired P_{CO_2} does not alter the pulmonary resistance if the ventilation is uncontrolled.

Since no consistent response to either of these interventions was obtained, it is unlikely that they are of any value in selecting patients for operation. It is of some interest that those patients who showed the greatest rise of pulmonary vascular resistance after administration of sodium bicarbonate to correct metabolic acidosis subsequently showed the greatest fall in pulmonary vascular resistance on breathing 100 per cent oxygen.

EFFECT OF INTERVENTIONS ON SYSTEMIC VASCULAR BED

Barratt-Boyes and Wood (1958) found that administration of 100 per cent oxygen in normal adult subjects resulted in a small but significant rise in systemic arterial mean pressure. Stroke index also rose significantly, but there was no overall change in cardiac index or systemic vascular resistance. In 1962 the rise in pressure was confirmed by two groups independently, but these workers also found that there was a significant rise in systemic vascular resistance, together with a rate related fall in cardiac output (Daly and Bondurant, 1962; Eggers *et al.*, 1962). The latter group found that these effects persisted for at least 40 minutes after oxygen was discontinued. The rise in systemic vascular resistance was confirmed in patients with congenital heart disease in several studies (Swan *et al.*, 1959; Marshall *et al.*, 1961; Krongrad *et al.*, 1973). However, Marshall and colleagues commented that this rise only occurred in patients under 12 years old. The younger patients in their report were studied under rectal tribromoethanol anaesthesia rather than sedation.

In the present study, rises and falls in systemic arterial mean pressure, blood flow, and resistance were found on breathing 100 per cent oxygen, and there was no significant overall change.

This variability of response was not explicable on the basis of age, systemic arterial oxygen saturation, or pulmonary vascular resistance. For this reason it seems unlikely that the variance with other reports can be explained on the basis of patient selection. In the same laboratory, using the same methods, systemic vascular resistance was found to rise significantly on administration of 100 per cent oxygen to patients with pulmonary atresia and ventricular septal defect (Macartney *et al.*, 1973). There is one possibly important difference between the present study and all the previous studies, which is that metabolic acidosis was corrected before administration of 100 per cent oxygen. Since tissue acidosis secondary to local hypoxia is an important cause of systemic vasodilatation, it is possible that some of the observed effects of 100 per cent oxygen have been the result of reduction of local hypoxia and therefore acidosis rather than of any direct effect. This might explain the persistent response found by Eggers *et al.* (1962) and the age-related response found by Marshall *et al.* (1961) (see above). Correction of the metabolic acidosis before giving oxygen would then diminish the vasoconstriction occurring with oxygen. However, though there was overall a rise in systemic vascular resistance on correcting metabolic acidosis, this did not achieve statistical significance.

Krongrad *et al.* (1973) in their study of patients with ventricular septal defect and truncus arteriosus stated that, 'the single most important change on breathing oxygen was the increase in systemic resistance'. While it is true that some of our patients had a lower pulmonary vascular resistance than theirs, the groups were broadly comparable, and our findings are at variance with this conclusion. The effect on pulmonary vascular resistance was far more striking and consistent than that on systemic vascular resistance.

RELATION OF PULMONARY TO SYSTEMIC VASCULAR RESISTANCE

The term 'resistance ratio' as used in the literature can refer either to the ratio of *total* pulmonary to systemic resistance (Swan *et al.*, 1959; Kirklin and DuShane, 1963; Kirklin, 1965; Cartmill *et al.*, 1966; Hallidie-Smith *et al.*, 1969; Krongrad *et al.*, 1973) or to the ratio between pulmonary and systemic *vascular* resistance, as is used here. In the context of pulmonary vascular obstructive disease without obstruction to pulmonary venous return, these differ very little, since both atrial mean pressures are very low compared with mean pulmonary and systemic arterial pressures. The use of resistance ratios has distinct advantages, since errors in oxygen capacity cancel out, oxygen uptake need not be measured, and indexing of flows and resistances, which has many theoretical and practical disadvantages (Morrison and Macartney, 1978) is made unnecessary. However, this study also highlights the shortcomings of resistance ratios.

Pulmonary vascular obstructive disease is progressive. Therefore any indirect measurement of its severity should be positively correlated with the age of the patients. In this study, pulmonary artery mean pressure and vascular resistance were so correlated, but the resistance ratio was not. Thus, though the resistance ratio may be helpful in acyanotic patients when pulmonary vascular disease is mild to moderate (Kirklin, 1965; Cartmill *et al.*, 1966), it probably is a poor measure of pulmonary vascular disease when this is severe. The reasons for this are complex. First, as previously indicated (Krongrad *et al.*, 1973) and shown in this study, systemic and pulmonary vascular resistance are positively correlated one with the other. On the other hand, chronic systemic hypoxia in congenital heart disease has recently been shown to result in a fall in systemic vascular resistance (Morrison and Macartney, 1978). Krongrad *et al.* (1973) found values of indexed systemic vascular resistance in their patients with pulmonary vascular disease considerably above their normal range, using an assumed oxygen uptake. The values of absolute systemic vascular resistance in the group of patients studied here, using a measured oxygen uptake, were not significantly different from the predicted normal value for patients with congenital heart disease, when the effects of body size, arterial oxygen saturation, premedication, and haematocrit were allowed for by stepwise regression analysis (Morrison and Macartney, 1978). Thus our results indicate no specific, direct, correlation between pulmonary and systemic vascular resistance. The correlation between the two may be simply the result of haematocrit, a rise in which increases resistance in both the systemic and pulmonary vascular beds. On the other hand, our group of patients had a somewhat lower mean systemic arterial oxygen saturation than that described by Krongrad *et al.* (1973), so that the effects of pulmonary vascular resistance and systemic arterial oxygen saturation in the systemic vascular bed in our group may have cancelled each other out. It should also be noted that comparisons between groups of patients with regard to indexed systemic vascular resistance are only valid if they are of comparable size. This is because indexing systemic vascular resistance does not completely correct for body size. As body size increases, so does indexed resistance (Morrison and Macartney, 1978).

Whatever the cause of these phenomena, it remains true that abrupt falls of systemic vascular resistance, such as occur with fevers or angiography, initiate a vicious spiral of arterial desaturation followed by further systemic vasodilatation and so on (Krongrad *et al.*, 1973).

Conclusion

Not all the original objectives of this study were achieved, but some unexpected and interesting findings were recorded. To some extent the need for evaluation of pulmonary vascular disease has diminished with advances in surgery. It has been shown that pulmonary vascular resistance may either continue to rise or fall after closure of ventricular septal defect in patients over 2 years of age, but on average it remains unchanged. However, if operation is carried out below 2 years of age, pulmonary vascular resistance postoperatively is normal, or almost so, regardless of its preoperative level (DuShane *et al.*, 1976). Now that primary repair of ventricular septal defect in infancy can be carried out with a low mortality (de Leval *et al.*, 1974), pulmonary vascular disease should become as rare in ventricular septal defect as it now is in atrial septal defect and persistent ductus arteriosus. To a lesser extent, because of high risks and a greater tendency to pulmonary vascular disease, the same is true for truncus arteriosus and transposition of the great arteries.

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Haemodynamic studies in veno-occlusive disease of the liver

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SUMMARY Haemodynamic studies in 8 tribal patients from central India with veno-occlusive disease of the liver are reported. The disease was caused by eating cereals contaminated with seeds of a crotalaria species rich in toxic pyrrolizidine alkaloids similar to monocrotaline and fulvine.

All patients showed raised hepatic venous wedge pressures and pressure gradients between hepatic venous wedge and free hepatic vein. Significant pressure gradients were also observed in the inferior vena cava. Right and left heart pressures were normal. Cardiac and stroke indices and ventricular work were significantly increased while systemic and pulmonary resistances were reduced. Hepatic blood flow was also reduced. Hepatic venograms were abnormal and the changes correlated well with the pressure gradients between hepatic venous wedge and free hepatic vein and with the histological changes in the liver.

Veno-occlusive disease of the liver in man caused by drinking concoctions prepared from indigenous plants containing pyrrolizidine alkaloids was described in detail by Bras *et al.* (1954) and Stuart and Bras (1957) from the West Indies. Minor outbreaks have also been reported by Willmot and Robertson (1920), Selzer and Parker (1951), Savvina (1952), and Braginskii and Bobokhodzhaev (1965). Outbreaks of veno-occlusive disease of the liver occurred recently in a tribal community of Central India and were caused by contamination of the staple cereal food with the seeds of a species of crotalaria, rich in toxic pyrrolizidine alkaloids similar to monocrotaline and fulvine (Tandon *et al.*, 1976). We were able to study 8 of these patients and describe their circulatory haemodynamics and hepatic venographic features. To our knowledge similar data have not been previously reported in English.

Subjects and methods

The 8 patients with venoocclusive disease of the liver (5 male and 3 female) were aged from 12 to 50 years (average 27 years) (Table 1). All presented with a history of pain in the epigastrium followed by rapid distension of the abdomen. All had significant ascites and 5 also had oedema of the feet. Mild jaundice was present in only 1 patient. The liver and spleen were palpable in 6

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Table 1 *Clinical features of veno-occlusive disease of liver*

Case no.	*Age (y)*	*Sex*	*Physical examination*				
			Jaundice	*Oedema*	*Ascites*	*Liver (cm below costal margin)*	*Spleen (cm below costal margin)*
1	24	F	Present	Absent	Mild	4·0	1·0
2	16	F	Absent	Absent	Moderate	5·0	1·0
3	25	M	Absent	Moderate	Moderate	6·0	1·0
4	12	M	Absent	Moderate	Moderate	4·0	1·5
5	20	M	Absent	Absent	Severe	Not palpable	Not palpable
6	35	F	Absent	Mild	Severe	Not palpable	Not palpable
7	30	M	Absent	Mild	Moderate	3·0	1·0
8	50	M	Absent	Mild	Moderate	3·5	1·5

Table 2 *Liver function tests in veno-occlusive disease of liver*

Case no.	*Bilirubin** (*μmol/l*)	*Total protein* (*g/l*)	*Albumin* (*g/l*)	*Globulin* (*g/l*)	*Alkaline phosphatase* (*KA units*)	*AST* (*SGOT*)† (*Karmen units*)	*ALT* (*SGPT*)†	*Sulphobromophthalein retention* (%)
1	51·3	74	18	56	18·0	60	35	6
2	10·3	70	18	52	16·0	90	50	3
3	18·8	74	18	56	25·0	80	80	15
4	17·1	74	18	56	28·0	70	35	4
5	23·9	63	26	37	8·0	55	30	30
6	12·0	51	25	26	8·0	100	60	35
7	5·1	72	35	37	8·0	40	32	20
8	10·3	76	32	44	7·0	30	28	4

AST, serum aspartate aminotransferase; ALT, serum alanine aminotransferase.
*Conversion factor for bilirubin: 1 μmol/l ≈ 0·058 mg/100 ml.
†Normal ranges: AST 40 units or less, ALT 35 units or less.

patients. There was no history of fever or bleeding from the gastrointestinal tract. None of the patients had clinical features of a hyperdynamic circulation. Of the 8 patients, 1 died 15 months after the onset of symptoms. The others recovered partially or completely.

Liver function tests (Table 2) showed lowered serum albumin and relatively high serum globulin levels. There was an abnormal sulphobromophthalein retention (>5%) in 5 of the 8 patients. Serum alkaline phosphatase levels were increased in 4 patients. Serum bilirubin was slightly increased in 3 patients. Serum aspartate aminotransferase (AST; SGOT) and serum alanine aminotransferase (ALT; SGPT) concentrations were slightly or moderately increased in all the patients.

Percutaneous liver biopsy showed almost identical changes in all patients. There were large areas of centrilobar haemorrhagic necrosis. The central vein was usually not recognisable, and in the biopsy specimens in which it was identified it was dilated and empty but invariably surrounded by sinusoids distended with blood. There was diffuse parenchymal injury and collagenisation of the sinusoids, and the reticulin framework showed collapse and duplication (Fig. 1). None of the livers was cirrhotic.

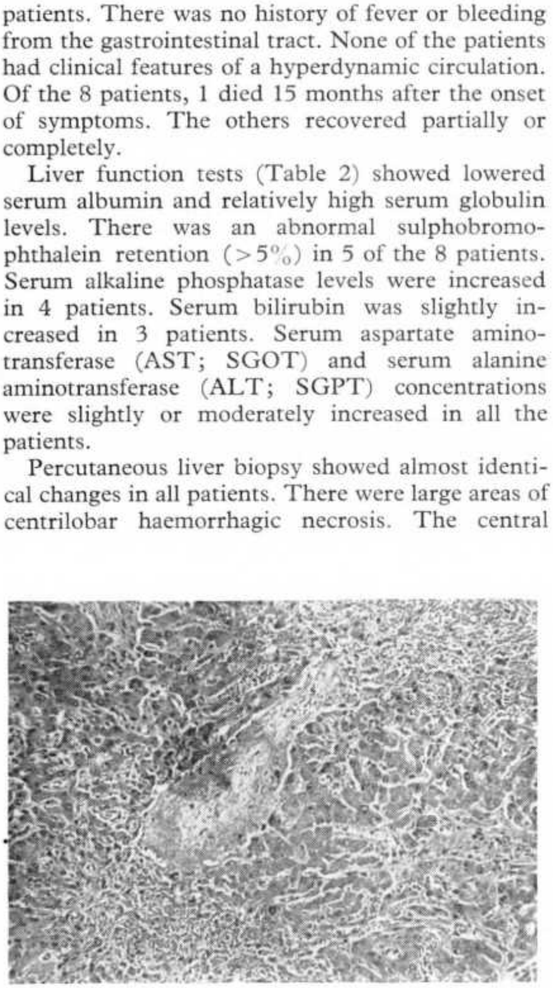

Fig. 1 *Liver biopsy from a patient with veno-occlusive disease of the liver. A centrilobular venous radicle is seen obliterated by proliferating fibroblasts and collagenous bundles. (H. and E. × 440.)*

Right heart catheterisation was carried out in the postabsorptive resting state in the supine position under light sedation (diazepam, 5 mg) using standard techniques. Informed written consent was obtained in all patients. The right brachial artery was cannulated for recording arterial pressure and dye dilution curves. Intracardiac pressures were recorded through Statham P23 AA pressure transducers on a 4-channel direct writing ink jet recorder (Elema-Schonander Mingograph). Baseline for all pressure measurements was mid-thorax (Roy *et al.*, 1957). Cardiac output was determined by the indicator dilution method (Hamilton *et al.*, 1932) from continuously recorded curves using a Colson's cuvette densitometer and a constant flow syringe with Evans Blue dye (5 mg) as the indicator. Vascular resistance, stroke index, and external left ventricular stroke work were calculated using standard formulae.

Hepatic venous wedge angiography after a hand injection of the contrast material and free hepatic vein angiography after pressure injection of Conray 420 were carried out in 4 patients. An inferior vena caval angiogram was also obtained in 1 patient. Hepatic blood flow was measured using indocyanine green dye in 4 patients (Caesar *et al.*, 1961). Free hepatic venous angiograms were graded according to the classification of Smith *et al.* (1971) which is as follows:

Grade I: Normal. Smoothly tapered hepatic veins with regular branches so that at least fifth order branching is demonstrated.

Grade II: Minimal loss of tapering and branching; sinusoidal filling is often normal.

Table 3 *Haemodynamic features of veno-occlusive disease of liver*

Case no.	*Heart rate (beats/min)*	*Flow*				*Mean pressure (mmHg)*				
		CI (l/min per m²)	*SI (ml per m²)*	*HBF (ml/min per m²)*	*HBF/CI (%)*	*RA*	*PA wedge*	*PA*	*BA*	*HV we*
1	88	5·9	66	784	13·3	5	7	20	85	24
2	88	8·0	91	1540	19·3	4	4	11	80	18
3	75	5·3	71	940	17·7	7·5	10	17	80	29
4	75	5·1	68	664	13·0	4	7	12	90	26
5	58	2·6	45	—	—	5	7	13	85	23
6	60	4·6	75	—	—	4	—	10	—	10
7	80	6·2	77	—	—	2	4	10	80	9
8	82	8·2	100	—	—	4	8	11	74	21

CI, cardiac index; SI, stroke index; HBF, hepatic blood flow; RA, right atrium; PA wedge, pulmonary artery wedge; PA, pulmonary artery; brachial artery; HV wedge, hepatic venous wedge; HV, free hepatic vein; IVC, inferior vena cava; SVR, systemic vascular resistance; PVR, pulmc vascular resistance; HVR, hepatic vascular resistance; LVSWI, left ventricular stroke work index; LVWI, left ventricular work index.
*Changes in hepatic vein wedge angiogram described in text (Smith *et al.*, 1971).

Grade III: Clear cut loss of branching, tapering, and sinusoidal filling.
Grade IV: Branching and tapering greatly reduced. Sinusoidal filling may still be present.
Grade V: Almost complete obliteration of hepatic venous system with no sinusoidal filling.

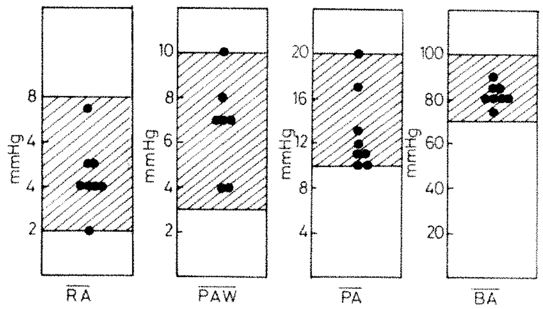

Fig. 2 *Mean right atrial ($\overline{RA}$), pulmonary arterial wedge ($\overline{PAW}$), pulmonary arterial ($\overline{PA}$), and brachial arterial ($\overline{BA}$) pressures were within normal range in patients with veno-occlusive disease of the liver. (Shaded areas denote normal pressures.)*

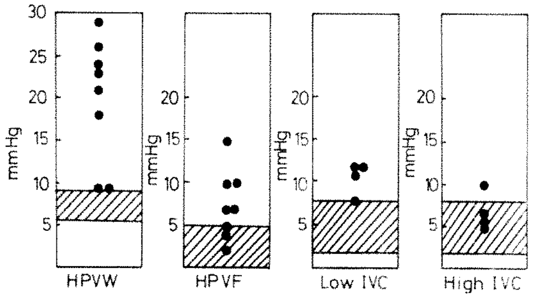

Fig. 3 *Mean hepatic venous wedge (HPVW), free hepatic vein (HPVF), and low inferior vena cava (IVC) pressures were raised in most patients, but high inferior vena caval pressures were usually normal.*

Results

The haemodynamic data are presented in Table 3.

PRESSURES (Table 3, Fig. 2 and 3)
Pressures obtained from the right atrium, right ventricle, pulmonary artery, pulmonary artery wedge, and brachial artery were within the normal range. Hepatic venous wedge pressures were, however, raised in all patients and ranged from 9 to 29 mmHg. Since the free hepatic vein pressure ranged from 3 to 15 mmHg, there was a significant pressure gradient between the hepatic venous wedge and free hepatic vein ranging from 5 to 19 mmHg. In 4 patients in whom inferior vena caval pressures were recorded, there was a pressure gradient between low and high inferior vena cava varying from 2·0 to 6·5 mmHg. In 2 patients, there was a significant pressure gradient between the free hepatic vein and inferior vena cava (4·0 and 5·0 mmHg, respectively).

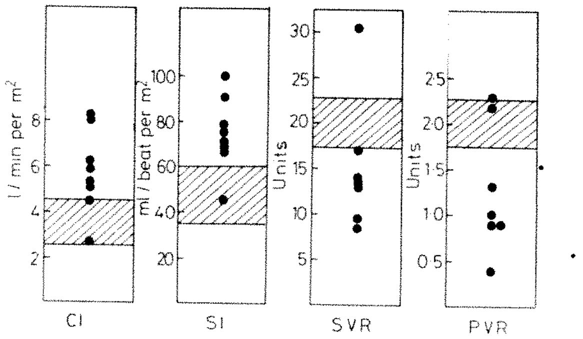

Fig. 4 *Cardiac (CI) and stroke indices (SI) were raised and the systemic (SVR) and pulmonary vascular resistances (PVR) were decreased in most patients.*

		Resistance (units × m^2)			*Work*		*Angiogram*	
IVC Low	*IVC High*	*SVR*	*PVR*	*HVR*	*LVWI* (*kg m/min per m^2*)	*LVSWI* (*g m/beat per m^2*)	*HV*	*HV wedge**
11	6·5	13·6	2·2	0·8	7·7	88	Grade III	Moderate
8	5	9·5	0·9	0·4	11·5	131	Grade III	Mild
12	10	13·8	1·3	0·5	6·4	85	Grade IV	Severe
12	5·5	16·9	1·0	0·8	7·1	95	Grade IV	Severe
—	—	30·7	2·3	—	3·7	64	—	—
9	4	—	—	—	—	—	—	—
—	—	13·6	1·0	—	9·4	118	—	—
—	—	13·9	0·4	—	4·1	148	—	—

FLOWS (Table 3, Fig. 4)
The systemic arterial oxygen saturation varied from 93 to 95 per cent. Cardiac index ranged from 2·6 to 8·2 l/min per m^2 and was higher than normal (more than 4·5 l/min per m^2) in 7 of the 8 patients. Since the heart rate was normal, the calculated stroke index was high.

RESISTANCE (Table 3)
The calculated systemic vascular resistance was low, ranging from 9·5 to 16·9 units × m^2 in 6 patients. Pulmonary vascular resistance ranged from 0·4 to 2·3 units × m^2, and was 1·0 or less in 4 patients.

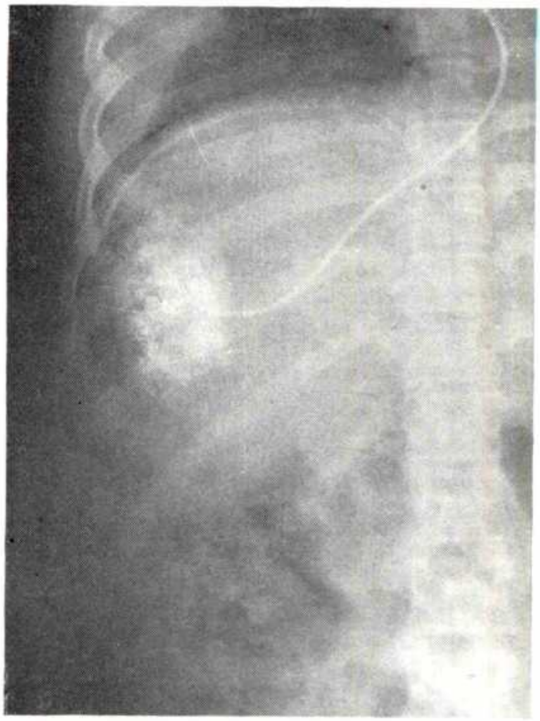

Fig. 5 *Hepatic venous wedge angiogram showing a very coarse nodular pattern of the sinusoids.*

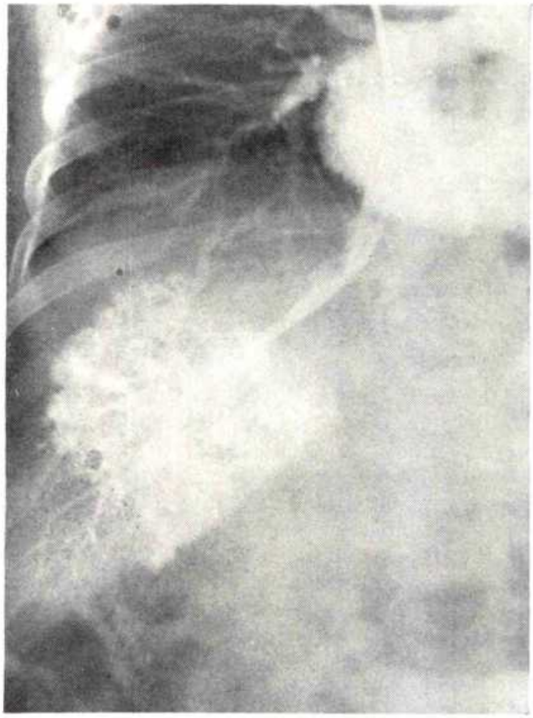

Fig. 6 *Free hepatic vein angiogram showing grade II changes with distinct loss of branching of the hepatic veins.*

LEFT VENTRICULAR WORK (Table 3)
Calculated left ventricular external work index was increased in 6 of the 7 patients in whom the data were available and ranged from 3·7 to 11·5 kg m/min per m^2. Stroke work index varied from 64·2 to 148·2 g m/beat per m^2.

HEPATIC BLOOD FLOW AND ANGIOGRAPHY (Table 3, Fig. 5 and 6)
Hepatic blood flow measurements were made in 4 patients. Effective hepatic blood flow was reduced in 3 and normal in 1 patient (normal: mean 1210 ml/min per m^2, range 1750 to 1960 ml/min per m^2). Hepatic blood flow expressed as a percentage of cardiac output was low in all (normal: mean 32%, range 28 to 36%). Hepatic vascular resistance was raised in 2 patients (cases 1 and 4) (normal: mean 0·47 units, range 0·40 to 0·59 units).

Hepatic vein wedge angiograms showed reversal of flow in the portal system as described in the early stages of portal cirrhosis (Smith *et al.*, 1971). A fine nodular pattern of sinusoids was noted in case 2 in whom there was a small pressure gradient between the hepatic venous wedge and free hepatic vein. In case 1, the nodular pattern was moderately coarse and in cases 3 and 4 it was very coarse (Fig. 5). Free hepatic vein angiograms showed grade II changes in case 2, grade III changes in case 1, and grade IV changes in cases 3 and 4 (Fig. 6). The most severe angiographic abnormalities were present in patients who had the largest pressure gradients between hepatic venous wedge and free hepatic vein. These patients also had histological evidence of extensive scarring indicating advanced disease. The inferior vena caval angiogram in case 1 showed a significant narrowing of the vein lumen at the level of the ninth thoracic vertebra.

Discussion

Circulatory changes in veno-occlusive disease of the liver have not been reported hitherto. The present study in 8 patients with histological evidence of veno-occlusive disease of the liver shows the presence of a hyperdynamic circulatory state. In addition, there are significant pressure gradients in the hepatic circulatory bed. Furthermore, though direct measurement of cardiac contractility have not been made, there is no evidence of myocardial dysfunction since the right and left heart filling pressures were normal and the stroke index and cardiac index increased. Cardiac abnormalities have not been shown histologically in veno-occlusive disease of the liver (Bras and Hill, 1956); this finding is consistent with the present haemodynamic observations. The hyperdynamic circulatory state was not clinically evident, but no explanation was found for this discrepancy.

While the toxic agent causing veno-occlusive disease of the liver has been identified as a pyrrolizidine alkaloid similar to monocrotaline and fulvine (Tandon *et al.*, 1976), the mechanism responsible for the high cardiac output in this disorder is not clear. McLean (1970) has shown experimentally that pyrrolizidine alkaloids can cause toxic injury to the hepatic veins and also cause pulmonary lesions. However, no data are available on the effect of these alkaloids on the other regional circulatory beds. One possible explanation for our findings is that the alkaloids may directly dilate the systemic vascular bed, which may in turn increase the cardiac output, but there are no experimental data to support such a concept. Mechanisms suggested to explain the high cardiac output state in other forms of liver disease, such as cirrhosis (Krook, 1956; Heinemann, 1960; Knauer and Lowe, 1967; Iwatsuki and Reynolds, 1973), may also be operative in veno-occlusive disease of the liver. Anaemia as a contributory factor can be ruled out in our patients as their haemoglobin levels were more than 10 g/dl and significant haemodynamic alterations in anaemia occur only at haemoglobin levels of 8 g/dl or less (Roy *et al.*, 1963).

Pressure gradients of 8·0 to 19·0 mmHg were observed between the hepatic wedge position and free hepatic vein. These are abnormal (Lundbergh and Strandell, 1973) but the findings are unlike those in portal cirrhosis where the pressure is raised in the hepatic venous wedge position but normal in the hepatic vein and inferior vena cava (Krook, 1956; Knauer and Lowe, 1967; Iwatsuki and Reynolds, 1973). A pressure gradient of 2 to 6·5 mmHg between the lower and upper segment of the inferior vena cava suggests that the veno-occlusive process could also extend into the inferior vena cava, though the gradient could also be the result of obstruction by thrombus formation or by an enlarged congested liver. The presence of obstruction, whatever its cause, was confirmed in 1 patient by an inferior vena caval angiogram which showed a significant narrowing of the lumen.

Hepatic vein angiograms are reported to be useful in the study of portal cirrhosis (Piper, 1961; Warren *et al.*, 1967). In veno-occlusive disease, it appears that there is a correlation between the pressure gradients between the hepatic venous wedge and free hepatic vein, the angiographic findings using the criteria of Smith *et al.* (1971), and the histological changes in the liver. Thus, in patients with small gradients, the angiographic abnormalities were mild or moderate while in those with higher gradients the angiographic and histopathological abnormalities were severe. The severity of these abnormalities may be dependent upon the amount of toxin ingested and perhaps also the pre-existing nutritional status.

Effective hepatic blood flow was reduced in 3 of the 4 patients in whom measurements were made, while the hepatic vascular resistance was increased in 2 of them. This may indicate a major intrahepatic shunting around the affected vessels. The variable findings may result from different degrees of involvement of hepatic veins and sinusoids. These observations need to be confirmed in a larger number of patients with veno-occlusive disease.

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Electrophysiological and haemodynamic basis for application of new pacemaker technology in sick sinus syndrome and atrioventricular block[1]

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SUMMARY A fundamental description of pacemaker systems which are commercially available or in clinical validation is given as a background for their application in a series of 62 consecutive patients presenting over a period of 1 year for permanent cardiac pacing. The patients (23 (37%) sick sinus syndrome, 38 (61%) atrioventricular block, and 1 ventricular tachycardia) were studied electrophysiologically and haemodynamically to allow the appropriate application of a pacemaker system. In sick sinus syndrome, 8 patients had permanent atrial pacing, 14 ventricular pacing, and 1 atrioventricular sequential pacing; in atrioventricular block, 8 patients had atrial synchronous ventricular inhibited pacing and the remaining 30 had ventricular pacing. A high incidence of atrial fibrillation, 9 patients, and abnormal sinus node function, 15 patients, precluded wider use of atrial synchrony. The results show benefit in acute haemodynamic studies of using systems including atrial sensing and/or pacing, and with greater availability of atrioventricular sequential and still more advanced pacemakers with dual sensing as well as dual pacing the majority of patients may be offered this benefit.

Permanent, implanted cardiac pacemakers have been used clinically since 1959 (Elmqvist and Senning, 1960). As is common with new treatments, the initial indications for use were very narrow, in this instance intended primarily for ventricular stimulation in cases of complete atrioventricular block with Adams-Stokes seizures. These early pacing systems maintained a constant regular cardiac rhythm by stimulating the ventricles asynchronously at a fixed rate, usually 70 pulses per minute. As a fuller understanding of cardiac pacing was realised, indications for use expanded to include management of symptomatic bradyarrhythmias, tachyarrhythmias, and restoration of optimal haemodynamics. As a result, the operational types of artificial pacemakers evolved so that there now exists an armamentarium of atrial and ventricular pacemaker systems, each appropriate to certain pathological situations within a broad range of cardiac diseases.

Several atrial pacemaker systems have been available for a number of years. Atrial lead stability difficulties, particularly, have limited their use and ventricular pacemakers are generally chosen even when the disease process appears confined to the atria. Recent reports, however, cite successful long-term results with transvenous atrial leads of several designs. These include: (a) J-shaped leads which wedge within the right atrium (Fields *et al.*, 1973), (b) smaller, tined J-shaped leads which are intended to be positioned within the right atrial appendage (Smyth *et al.*, 1976; Kleinert *et al.*, 1977), (c) hooking electrodes (Rosenkranz and Schaldach, 1971; Irnich *et al.*, 1972), (d) 'screw-in' electrodes (Kleinert and Bisping, 1977), and (e) coronary sinus leads (Greenberg *et al.*, 1978; Moss and Rivers, 1978). With the development of transvenous atrial leads which promise long-term efficacy, reassessment of the type of pacemaker system best suited to each patient is appropriate.

The object of this report is to provide a fundamental, generic description of pacemaker systems which are commercially available or in clinical validation and their indications for use, followed by clinical experience in selection and application of these systems.

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[1] Part of this paper was presented to the British Cardiac Society, November 1977, under the title, 'Pacing for optimal function in the spectrum of sick sinus syndrome and atrioventricular block'.

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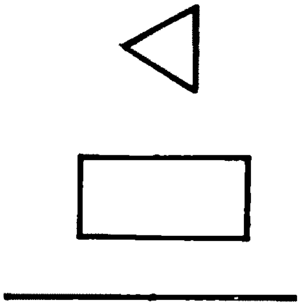


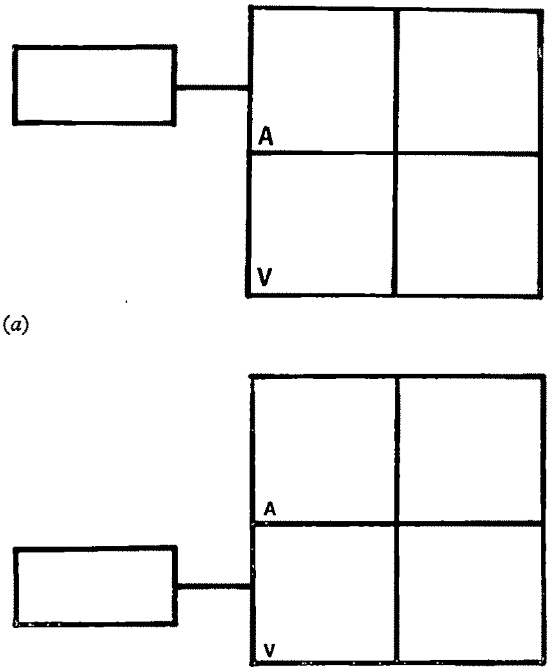
Fig. 1 *A diagrammatic representation of an amplifier (triangle), oscillator (rectangle), and lead (line).*

Description of pacing systems

Implantable cardiac pacemakers consist of many components including an energy source, electronic circuits, mechanical package, and heart leads. While *in vivo* performance characteristics rely heavily on the careful integration of all constituent parts, for present purposes we may consider the majority of available pacemakers to consist of 3 interactive functional elements: (1) the stimulation pulse forming network or oscillator; (2) the cardiac activity sensing portion or amplifier; (3) the lead system used to connect the pacemaker and the myocardium.

Fig. 1 shows the schematic representation for these elements as used in this report.

Identification of the pacing systems to be discussed is simplified considerably by the use of the generic code originally suggested by Parsonnet *et al.* (1974). The code consists of a sequence of three characters which describe the characteristics of the pacemaker. The first character identifies the *chamber paced*—A for atrium, V for ventricle, D for dual chamber pacing. The second character identifies the chamber sensed—A for atrium, V for ventricle, D for dual chamber sensing. The third character denotes the mode of response, if applicable—I for *inhibited* or blocked output in response to a sensed signal, T for a triggered or synchronised output. 'O' is used where the identification comment is not applicable. A VOO designation, therefore, would describe a ventricular stimulating device which does not sense intrinsic activity and thus does not modify its output in response to spontaneous activity. A VAT designation describes a ventricular stimulating pacemaker whose output is triggered by sensed atrial electrograms.



(*a*)

(*b*)

Fig. 2 (*a*) *A four-chambered heart diagram with an oscillator connected by a lead to an atrium (A); (V) denotes ventricle. This constitutes an AOO pacemaker system.* (*b*) *A VOO system, an oscillator connected by a lead to a ventricle (V). (A) denotes atrium.*

(A) Asynchronous pacemaker systems

The asynchronous pacemaker system is the most fundamental of the commercially available devices, consisting of a pulse forming network and a lead system. The purpose of this device is to provide a fixed rate train of stimuli to the atria (AOO Fig. 2a) or ventricles (VOO Fig. 2b) irrespective of and unresponsive to any intrinsic cardiac activity. Since the VOO and AOO device's output is so regular, this type of device is often incorrectly referred to as a fixed rate pacemaker instead of an asynchronous pacemaker.

While this report is primarily concerned with fully implanted pacemaker systems, it may be appropriate to digress at this point to discuss briefly radio-frequency coupled asynchronous pacing systems. These consist of a small, implanted, passive receiver/decoder to which the heart leads are connected, and an external battery-powered transmitter which is used to power and programme the receiver. Systems of this configuration received much attention in the early days of pacing as the implanted portion was significantly smaller than self-contained implanted devices because of the absence of batteries (Glenn *et al.*, 1959; Cammilli *et al.*, 1962). Consequently, these systems offered the potential of increased reliability and reduced patient exposure to repeated surgery. Improvements in implantable pacemaker design, however, obviated most of the benefits of these systems. Recently, renewed interest in these devices has been noted for the physician/patient management of episodic refractory tachycardias with rapid pacing (Iwa and Wada, 1974; Kahn *et al.*, 1976; Waxman *et al.*, 1978).

CLINICAL APPLICATION

Atrial asynchronous pacemaker (AOO)

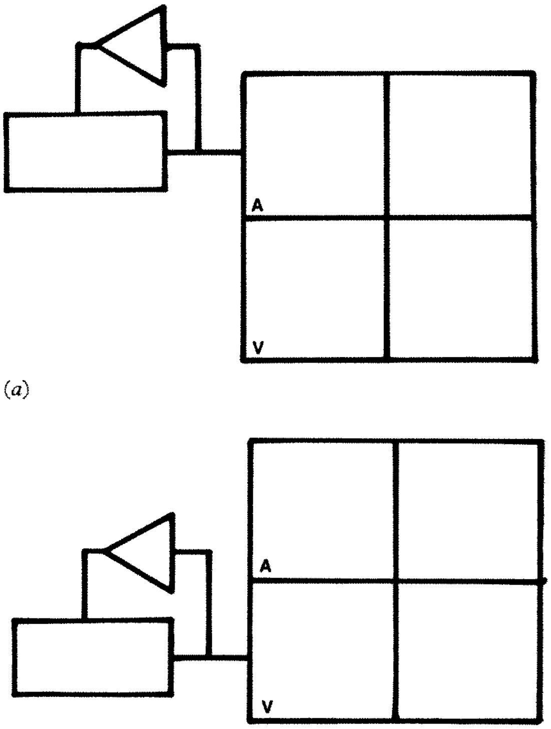
Clinical use of AOO devices is rarely indicated. This type of pacemaker may find limited use in patients concurrently showing (1) stable sinus bradycardia or absolute pacemaker dependence; the latter was not seen in the present series (see below), (2) a normal His-Purkinjesy stem, and (3) improved haemodynamics with temporary atrial versus ventricular pacing. Atrial pacing is specifically contraindicated in cases of atrial paralysis (Sutton *et al.*, 1977).

Ventricular asynchronous pacemaker (VOO)

VOO pacemakers may be indicated in patients with complete atrioventricular block, showing no intrinsic competitive rhythms and pacemaker dependence. Those with complete anterograde *and* retrograde atrioventricular block and sinuatrial node dysfunction manifest as sinus bradycardia, sinuatrial block, or atrial fibrillation may also be candidates for this form of pacing. The occurrence of retrograde atrioventricular atrial activation upon ventricular stimulation results in an inappropriate contraction sequence which may cause pronounced hypotension in some patients. Further, patients considered for VOO pacing should be those who would benefit little on haemodynamic grounds or because of general infirmity from more sophisticated pacemaker types. Less than 5 per cent of patients are estimated to be candidates for VOO pacemakers (Fontaine *et al.*, 1978); one patient was found to be pacemaker dependent in this series (see below).

(B) Demand pacemaker systems

While a subset of patients exhibiting stable bradyarrhythmias such as those with complete third degree atrioventricular block exists, a majority of patients have periods of spontaneous cardiac activity during which artificial pacing may be inappropriate. Lacking any means with which to sense intrinsic cardiac activity, asynchronous pacemakers may, therefore, compete with spontaneous rhythms. Competitive pacing may produce symptomatic hypotension, ventricular tachycardia, and possibly ventricular fibrillation (Furman and Escher, 1970). By providing a properly designed cardiac electrogram sensing element (amplifier) as shown in Fig. 3a and 3b, the pacemaker can be made to be responsive to intrinsic activity. In the absence of a sufficiently rapid spontaneous cardiac rhythm, the demand pacemaker produces stimuli at a preset fixed rate (nominally 1000 ms to 800 ms interstimulus or escape interval). Electrograms detected by the amplifier modify the basic escape interval of the oscillator in one of two ways. In the case of *inhibited* demand devices, electrograms occurring and detected within the interstimulus interval reset the oscillator so that the next pacemaker stimulus occurs at the preset escape interval following intrinsic activity (Fig. 4). No stimuli are produced when the intrinsic rate is greater than the preset rate of the pacemaker (that is, electrogram to electrogram interval is shorter than the pacemaker escape interval). When spontaneous activity is



(*a*)

(*b*)

Fig. 3 (*a*) *An atrial demand pacemaker AAI or AAT; (A) atrium, (V) ventricle.* (*b*) *A ventricular demand pacemaker VVI or VVT; (A) atrium, (V) ventricle.*

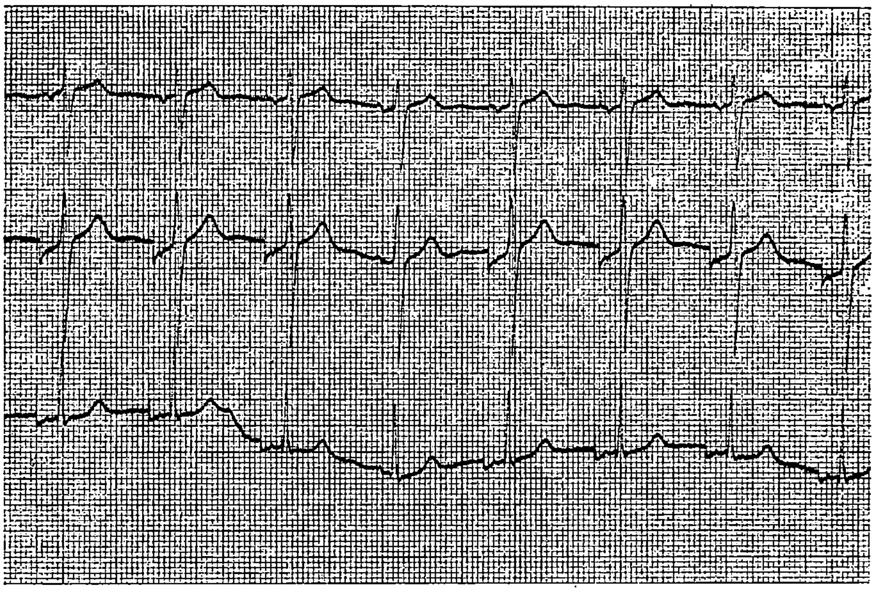


Fig. 4 *A three-lead electrocardiogram. An AAI pacemaker stimulates the atrium in the first 3 beats. There is a spontaneous depolarisation at the fourth beat which inhibits the pacemaker. Atrial stimulation continues after the escape interval.*

faster than the pacemaker escape interval in *triggered* demand pacemakers, an output stimulus occurs within the spontaneous electrogram during the absolute refractory period of the tissue (Fig. 5). Demand pacemakers of the triggered or inhibited types may be applied to either the atria (Fig. 3a) (AAT, AAI), or to the ventricles (Fig. 3b) (VVT, VVI). While atrial and ventricular demand pacemakers are functionally identical, electrical specifications and characteristics of the sensing circuitry may be modified to accommodate the intended application (Moss, 1975).

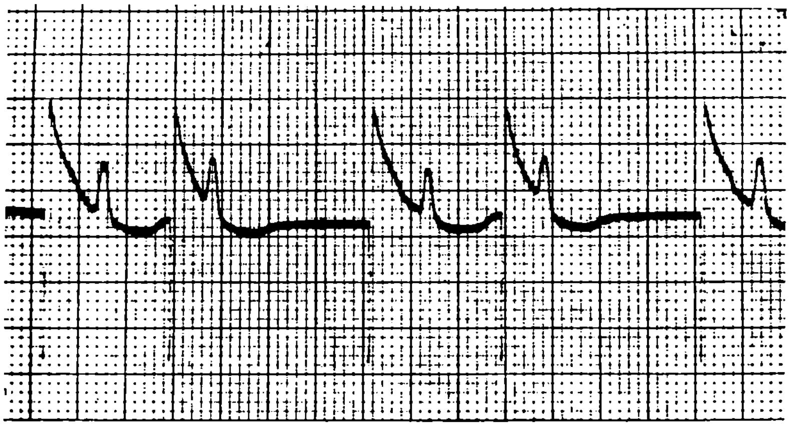


Fig. 5 *An electrocardiogram of an AAT pacemaker. The first, third, and fifth are pacemaker induced atrial beats. The second and fourth are spontaneous atrial beats which illustrate the triggered mode. Note the pacemaker-induced beats have a stimulus to QRS interval of 200 ms while the spontaneous complexes have a stimulus to QRS interval of 120 ms.*

CLINICAL APPLICATION

(1) *Atrial demand pacemakers (AAI, AAT)*
Pacemakers of this type are indicated in sick sinus syndrome[1] with no attendant His-Purkinje disease where haemodynamics are improved by the atrial contribution to cardiac output versus ventricular pacing (Benchimol *et al.*, 1965; Samet *et al.*, 1966; Befeler *et al.*, 1971). During episodes of atrial tachycardia, these devices are ineffective, the AAI being inhibited by the rapid rate and, correspondingly, the AAT pacemaker discharging ineffectively in the P wave. Since these tachycardias represent escape rhythms consequent upon episodes of sinus bradycardia or sinuatrial block (Haft, 1974), prevention of slow rhythms by the pacemaker with administration of antiarrhythmic agents often results in reducing the incidence of atrial tachycardia (Moss and Davis, 1974). Particular improvement in haemodynamic performance with atrial pacing may be obtained in cases when ventricular pacing results in retrograde atrioventricular conduction (Furman, 1973). Atrial pacing is contraindicated in atrial paralysis (Sutton *et al.*, 1978).

(2) *Ventricular demand pacemakers (VVI, VVT)*
Ventricular demand pacemakers are indicated in complete atrioventricular block where periods of normal conduction or spontaneous ventricular rhythms may exist and where the haemodynamic benefit of atrial systole is judged to be unnecessary, either on the grounds of no improvement in cardiac function or where the patient is dominantly in sinus rhythm without severe delay in ventricular conduction (Paeprer *et al.*, 1977). Use in sick sinus syndrome may be indicated where there is no retrograde atrioventricular conduction with ventricular stimulation, and where there is no clinically significant haemodynamic benefit to be obtained with more sophisticated atrioventricular pacing systems, and when atrial fibrillation is the dominant atrial rhythm. Demand systems, in particular the VVI, are indicated because patients with atrial fibrillation may manifest faster rhythms than those of the pacemaker in response to physiological situations such as exercise.

(C) Atrial synchronous pacemaker systems

During periods of stimulation using asynchronous or demand ventricular devices (VOO, VVT, VVI) in the absence of retrograde atrioventricular conduction or atrial fibrillation, atrioventricular dissociation exists (Fig. 6). In the majority of patients with normal sinus node function treated with ventricularly programmed pacemakers, the cardiac output loss resulting from atrioventricular dissociation does not manifest itself clinically. However, the clinical course in patients with a limited ability to augment ventricular stroke volume in response to physical activity, or those with ventricular pacemaker induced tachyarrhythmias (Kastor and Leinbach, 1973; Waxman and Wald, 1977), may be much improved by synchronising ventricular stimulation to atrial systole, thereby taking advantage of the atrial contribution to cardiac output and physiological heart rate change (Nathan *et al.*, 1963; Samet *et al.*, 1965; Karlöf, 1975). The atrial (P wave) synchronous pacemaker (VAT) consists of an atrial sensing amplifier and a ventricular stimulating oscillator arranged and connected to the heart as shown in Fig. 7. Each time an atrial electrogram is detected, the ventricular oscillator is triggered, producing a stimulus

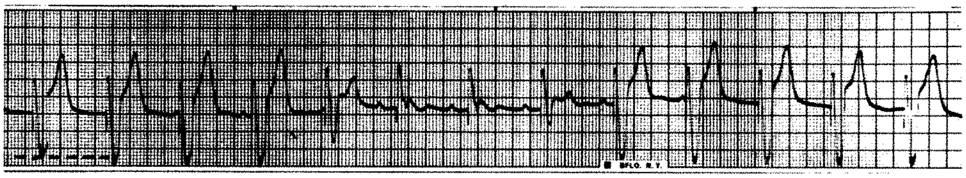


Fig. 6 *A VVT pacemaker electrocardiogram. Atrioventricular dissociation exists during the first 4 complexes followed by a fusion beat, 3 sinus conducted beats on which a pacemaker stimulus falls in the absolute refractory period, and the strip ends with 5 complexes of ventricular pacing with atrioventricular dissociation.*

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[1] A single, generally accepted description of sick sinus syndrome does not exist at present. In this text sick sinus syndrome is defined as a disease of the specialised conducting system of the heart which is manifest primarily in abnormal discharge of the sinuatrial node resulting in sinus bradycardia (< 60/min) and sinuatrial block. Consequent upon the bradyarrhythmias are frequent escape rhythms, some of which are tachycardiac, including atrial tachycardia, flutter, and fibrillation. Frequently the ventricular conduction system is partially involved in the disease process. The patient may present with syncope, palpitation, or dyspnoea as specific symptoms. Syncopal episodes may be typical Adams-Stokes seizures or attacks of longer duration which may simulate variants of epilepsy and transient cerebral ischaemic episodes.

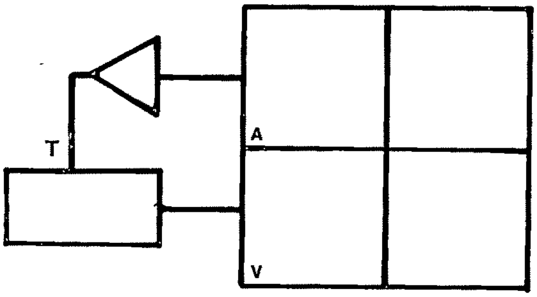

Fig. 7 *A VAT pacemaker. (A) atrium, (V) ventricle, (T) triggering amplifier.*

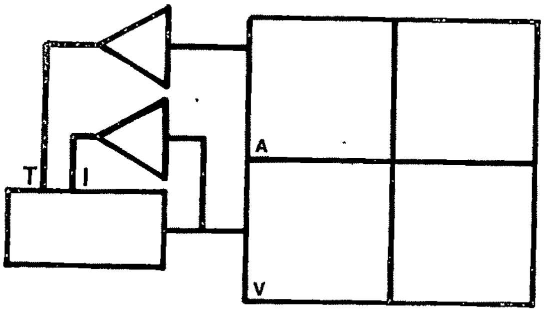

Fig. 9 *An atrial synchronous ventricular inhibited pacemaker* $VD\,\frac{T}{I}$. *(A) atrium, (V) ventricle, (T) triggering amplifier, (I) inhibiting amplifier.*

after an interval which mimics the normal atrioventricular delay interval (Fig. 8). In the absence of sensed atrial electrograms which may result from atrial lead displacement, during atrial fibrillation or sinus arrest, the atrial synchronous pacemaker operates as an asynchronous ventricular pacemaker (VOO) at a preset basic rate. A significant shortcoming of atrial synchronous devices (VAT) is their inability to sense and respond to spontaneous ventricular activity. Several atrial synchronous pacemaker-induced arrhythmias have been shown and suggested (Castellanos *et al.*, 1968).

An evolutionary version of the atrial synchronous device (VAT) which offers a potential for minimising previously reported induced arrhythmias is shown in Fig. 9. In addition to the functional elements of the VAT pacemaker, this device VD $\frac{T}{I}$[1] has a second sensing amplifier intended to sense intrinsic ventricular activity and inhibit the ventricular oscillator when necessary. In the absence of sensed atrial electrograms, the VD $\frac{T}{I}$ functions as an inhibited ventricular demand pacemaker (VVI). During periods of normal sinus rhythm, without normal ventricular response, this device behaves as a VAT pacemaker. When normally conducted ventricular complexes or ventricular ectopic activity occurs, the VD $\frac{T}{I}$'s oscillator is inhibited for that cycle in a manner similar to a VVI device.

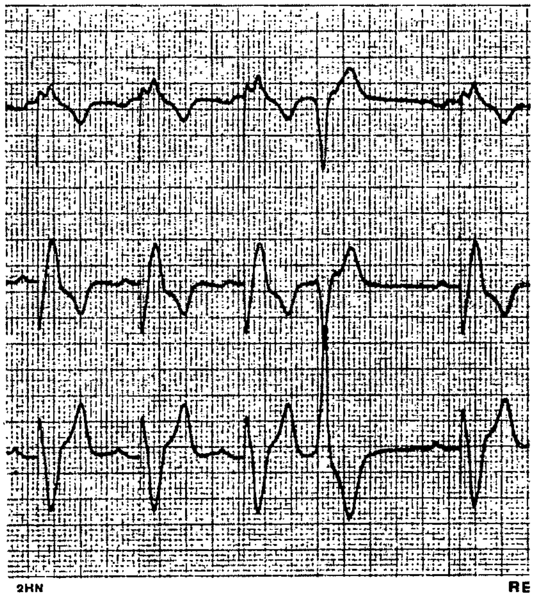

Fig. 8 *A 3-lead electrocardiogram of an atrial synchronous pacemaker. The first 3 beats show atrial synchrony inhibition of the ventricular oscillator. The last beat shows atrial synchrony (*$VD\,\frac{T}{I}$ *pacemaker).*

CLINICAL APPLICATION

Atrial synchronous pacemakers (VAT, VD $\frac{T}{I}$)

Atrial synchronous pacemakers are indicated in complete or intermittent heart block with normal sinus node function where the haemodynamic benefit of the properly timed atrial systole is necessary or worth while (Karlöf, 1975). These patients should show atrioventricular block frequently and are most suitable if atrioventricular block develops on exercise. Atrial synchronous devices are contraindicated in sick sinus syndrome or atrial fibrillation. Excessively late retrograde atrial activation upon ventricular stimulation may

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[1] *Note:* The third symbol of the generic nomenclature code has been modified to include more advanced pacemakers.

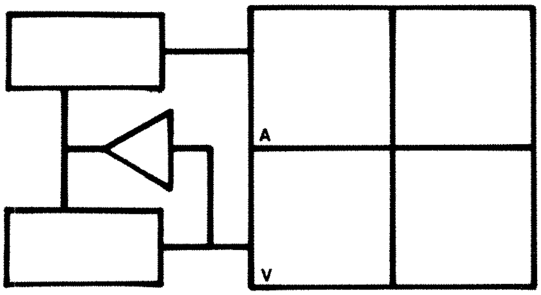

Fig. 10 *An atrioventricular sequential pacemaker DVI. (A) atrium, (V) ventricle.*

result in pacemaker-induced tachycardia and, therefore, the suitability of specific pacemaker designs must be assessed in patients with retrograde conduction.

(D) Atrioventricular sequential pacemakers

The VAT type device maintains atrioventricular association in patients with normal sinus rhythms within the operational specifications of the pacemaker. Maintenance of the atrioventricular contraction sequence in patients with sinus node dysfunction, primarily bradycardias, may be accomplished with a DVI pacemaker as shown in Fig. 10. Both oscillators in this pacemaker configuration are inhibited by the ventricular electrogram only. If no ventricular activity is sensed within the escape interval of the atrial oscillator, a stimulus is delivered to the atria. If ventricular activity is then not sensed within a preset atrioventricular delay interval, the ventricular oscillator produces a ventricular stimulus. Conducted ventricular beats or ectopic ventricular activity inhibit and reset both oscillators (Fig. 11).

CLINICAL APPLICATION

Atrioventricular sequential pacemaker (DVI)
DVI pacemakers are indicated in sick sinus syndrome with accompanying His-Purkinje disease or in atrioventricular block with accompanying evidence of abnormal sinus node function where haemodynamic benefit from correctly placed atrial systole is shown. Further, DVI pacing may have application in the overdrive of atrial and ventricular ectopic rhythms and re-entry tachyarrhythmias (Fields *et al.*, 1973).

Patients and methods

Since many of the barriers to using atrial systems have been effectively overcome, 62 consecutive patients presenting for permanent pacing at Westminster Hospital, London, between February 1977 and February 1978, have been studied for selection of optimal pacing system. There were 40 men and 22 women, mean age was 64 years (range 51 to 89). Twenty-three patients who were syncopal or near syncopal had sick sinus syndrome diagnosed on routine electrocardiography and/or Holter monitoring and 38 had atrioventricular block with syncopal episodes or heart failure. One was given ventricular pacing for overdrive

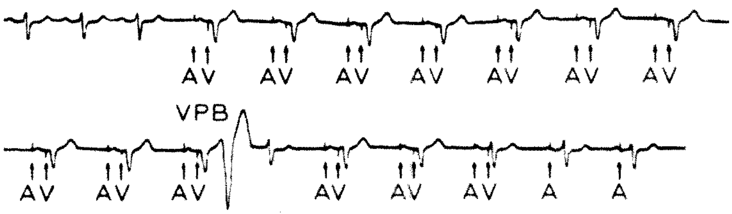

Fig. 11 *An electrocardiogram of an atrioventricular sequential pacemaker DVI. The 2 strips are not continuous. The first 3 complexes in the upper trace show sinus rhythm without atrioventricular block, both oscillators are inhibited; the remaining complexes show atrioventricular sequential pacing. The lower trace shows atrioventricular sequential pacing in the first 3 complexes. There then follows a ventricular premature beat (VPB) which inhibits both oscillators; the next beat is sinus conducted which also inhibits both oscillators. The sixth and seventh complexes show atrioventricular sequential stimulation and the eighth complex shows atrial stimulation and ventricular fusion between normal conduction and ventricular stimulation. The ninth complex shows inhibition of the ventricular oscillator with the atrial stimulus falling in the atrial absolute refractory period. (A) Atrial stimulus, (V) ventricular stimulus.*

of ventricular tachycardia. All patients underwent a 24-hour period of Holter monitoring and an exercise stress (submaximal) using a bicycle ergometer. In the patients with sick sinus syndrome and with atrioventricular block, sinus node recovery time and His bundle electrograms were recorded, omitting those with atrial fibrillation. A haemodynamic study was performed on all patients except those with atrial fibrillation and those with atrioventricular block in whom abnormal sinuatrial function was shown. Measurements included pulmonary capillary wedge, pulmonary artery, and aortic pressures, and cardiac output measured by the thermodilution technique. These were recorded during the patient's own rhythm, which was sinus bradycardia (in sick sinus syndrome) or complete atrioventricular block, during ventricular pacing at 70/min, and during either atrial pacing at 70/min for patients with sick sinus syndrome or atrioventricular pacing (DVI) for patients with atrioventricular block. After the haemodynamic study the sinus node recovery time was repeated after administering atropine 1·2 mg intravenously. In cases of atrial fibrillation and when sinuatrial node function was abnormal in the atrioventricular block group, the patients proceeded directly to permanent ventricular pacing. The latter group would now receive a DVI pacemaker, but during this series supplies of this unit were not freely available. During ventricular pacing absence of retrograde atrioventricular conduction was shown using an atrial electrogram.

The results of these physiological studies were used to select the type of pacemaker for permanent implantation.

Results of physiological studies

Of the 23 patients with sick sinus syndrome, who constituted 37 per cent of the whole group, 8 displayed optimal haemodynamics and were suitable electrophysiologically for atrial pacing using a rate adjustable AAI (Medtronic 5963A) or a non-rate adjustable AAI (Medtronic 5951AD) pacemaker. Fourteen had no haemodynamic benefit from atrial pacing or were either electrophysiologically unsuitable for atrial pacing or showed atrial fibrillation as their dominant rhythm. They received permanent VVI ventricular stimulators (Medtronic 5973; Telectronics P150B, CPI 0502, 0505; Vitatron C2120). One patient (case 5, Table 1) required atrial pacing on the basis of the haemodynamics but showed severe His-Purkinje system disease also and this required DVI atrioventricular sequential pacing (Medtronic 5992). The electrophysiological results are shown in Table 1. The

Table 1 *Electrophysiological and haemodynamic data in sick sinus syndrome*

Case no.	*SNRT*	*HV*	*Retrograde atrioventricular conduction*	*Cardiac output (l/min)*			*Pacer type*
				Own rhythm	*Atrial pacing (70/min)*	*Ventricular pacing (70/min)*	
1	Abnormal	Normal	+	3·86	4·42	3·25	AAI
2	Abnormal	Normal	+	3·67	—	3·43	VVI
3	Abnormal	Normal	+	4·66	5·47	3·38	AAI
4	Abnormal	Abnormal	0	3·17	—	3·13	VVI
5	Abnormal	Abnormal	0	4·01	3·55*	2·63	DVI
6	Abnormal	Normal	+	4·18	5·26	4·08	AAI
7	Abnormal	Normal	+	—	—	—	VVI
8	Abnormal	Normal	+	2·87	2·51	2·75	AAI
9	Abnormal	Normal	+	5·75	6·80	6·02	AAI
10	Abnormal	Normal	+	2·60	3·90	3·19	VVI
11	AF	Normal	0	—	—	—	VVI
12	AF	Normal	0	—	—	—	VVI
13	Abnormal	Normal	+	4·47	5·18	4·38	AAI
14	AF	Normal	0	—	—	—	VVI
15	Abnormal	Normal	0	7·37	5·42	5·51	VVI
16	AF	Normal	0	—	—	—	VVI
17	Abnormal	Normal†	+	—	—	—	VVI
18	Abnormal	Normal	0	4·42	4·28	3·95	VVI
19	AF	Normal	0	—	—	—	VVI
20	Abnormal	Normal	+	3·59	3·76	3·22	AAI
21	Abnormal	Normal	+	3·43	3·61	3·00	AAI
22	Abnormal	Normal	+	4·18	4·77	3·24	AAI
23	Abnormal‡	Normal	+	7·92	7·18	6·27	VVI

*DVI pacing at 70/min.
†Bifascicular block on scalar electrocardiogram.
‡Sinus rhythm consistently greater than 70/min.
SNRT Sinus node recovery time; AF, atrial fibrillation.

sinus node recovery time was more than 150 per cent of control at switch-off from atrial pacing at 140 ppm in all patients before and after atropine. Low right atrium (A) to His time was less than 200 ms in all patients.

The His to ventricular time was between 35 and 55 ms in all except case 4 where it was 60 ms, and case 5 where it was 85 ms. The presence of retrograde atrioventricular conduction was variable but, when present, was one feature in determining the need for atrial rather than ventricular permanent pacing.

The haemodynamic results in 16 of these 23 patients are presented also in Table 1. Only the cardiac outputs are shown. The type of pacemaker implanted is indicated in the right hand column of the figure. Cases 2 and 4 were studied early in the series when the chief criterion for ventricular pacing was that no fall in output occurred between the patient's own rhythm and ventricular pacing. As this was not the case in these 2 patients, atrial pacing outputs were not performed. The choice of pacemaker in case 5 was discussed above. Generally atrial pacing was shown to have an advantage over ventricular pacing. These improvements did not reach statistical significance; however, when left ventricular filling was also taken into account and ventricular function curves were plotted a statistically significant ($P < 0\cdot05$) improvement of atrial over ventricular pacing was found (Sutton and Perrins, 1979). Only cases 8 and 15 showed no improvement with atrial pacing over ventricular pacing; in retrospect, cases 2 and 4 may have derived benefit from atrial pacing rather than ventricular. Case 7 was not studied haemodynamically because atrial pacing for sinus node recovery time caused an Adams-Stokes attack. Resuscitation was accomplished by instituting ventricular pacing immediately. Case 10 was considered most suitable for atrial pacing; however, atrial thresholds in excess of 4 V at 1·0 ms were found in the right atrial appendage. Therefore, ventricular pacing was used. Cases 11, 12, 14, 16, and 19 showed atrial fibrillation as their dominant rhythm and were for this reason not studied haemodynamically. Case 17 was given ventricular pacing because of the existence of bifascicular block (right bundle-branch block and left anterior hemiblock) despite a normal His-ventricular time. Case 23 showed better cardiac output with atrial pacing than ventricular but because his dominant rhythm was sinus at a rate of greater than 70 ppm, ventricular pacing was chosen. Ventricular pacing in sick sinus syndrome can be associated with severe haemodynamic changes (Blömer *et al.*, 1977; Patel *et al.*, 1977). Arterial pressure may fall at the onset of ventricular pacing taking over from sinus rhythm, a finding also made in patients with atrioventricular block. The latter patients usually recover their arterial pressures within a few cardiac cycles. However, in sick sinus syndrome, recovery may be incomplete or not exist and falls of 70 or more mmHg in arterial pressure may be seen. Appropriately timed retrograde atrioventricular conduction is probably the major factor and when the pulmonary capillary wedge pressure is observed during retrograde atrioventricular conduction a high systolic wave can be observed. This is, of course, superimposition of the 'a' wave generated by the retrograde atrioventricular conduction upon the normal 'v' wave occurring at that time.

Two patients before this series experienced Adams-Stokes attacks during ventricular pacing which was shown to be the result of retrograde atrioventricular conduction causing hypotension. In each case normal ventricular pacing was observed during the Adams-Stokes attacks. Both patients were converted to atrial pacing. In the first, complete abolition of attacks was achieved; in the second, control was obtained using a temporary atrial lead. This lead subsequently displaced with loss of atrial pacing and an Adams-Stokes attack. Resuscitation was unsuccessful. Two patients in this series (cases 2 and 17) also experienced episodes of severe hypotension during retrograde atrioventricular conduction. In case 2 a coincident atrioventricular bypass tract was considered responsible (Waxman and Wald, 1977). Control was obtained by use of a beta-blocking drug. Case 17 had retrograde atrioventricular conduction blocked by a beta-blocking drug with symptomatic relief. Both of these patients would now be considered for a DVI pacemaker (Fields *et al.*, 1973).

Of the 38 patients with atrioventricular block, comprising 61 per cent of the whole group, only 10 patients had normal sinuatrial node function. Of these, 8 were fitted with atrial synchronous ventricular inhibited VD $\frac{T}{I}$ pacemakers (Medtronic 5993) using an endocardial right atrial lead for sensing atrial activity (Medtronic 6991—7 patients, and transvenous endocardial screw-in lead Medtronic SP0039BV—one patient). The remaining 2 were in dominant sinus rhythm with rare episodes of atrioventricular block which was specifically not induced by exercise. Atrial fibrillation was either permanent or intermittent in 9 patients and at study a further 15 patients showed evidence of abnormal sinuatrial node function either on routine electrocardiography, Holter monitoring, exercise, or abnormal sinus node recovery times, or a com-

Table 2 *Haemodynamic data in atrioventricular block*

Case no.	*Own rhythm*	*CO l/min VP 70/min*	*DVI* 70/min*
1	4·09	3·76	5·07
2	3·94	4·54	4·32
3	4·02	2·98	3·60
4	5·93	5·09	5·61
5	3·62	3·62	4·27
6	3·35	4·20	4·95
7	4·01	3·51	4·23
8	5·68	4·26	5·42

*External $VD\frac{T}{I}$ was not available for these studies. Therefore, an external DVI was used with fixed PR 0·20 ms.

bination of these. One patient showed retrograde atrioventricular conduction which constituted a contraindication to use of an atrial synchronous pacemaker. Three patients were not studied because of general frailty or other complicating conditions. Thus 74 per cent of patients with atrioventricular block were unsuitable for atrial synchronous pacing. All these patients received ventricular stimulators; in retrospect, some of these may have received benefit from DVI atrioventricular pacing. The haemodynamic results of the 8 patients with normal sinuatrial node functions are shown in Table 2. The second patient showed little benefit from atrial systole at rest. However, his exercise performance was greatly increased after atrial synchronisation. The exercise studies were made separately without haemodynamic measurements. At left ventricular angiography his ejection fraction was 20 per cent with generally impaired wall motion and his coronary arteries were normal. The inferred aetiology of his conduction tissue disease is, therefore, cardiomyopathy. Case 4 was in sinus rhythm at the time of study. It is considered that this offers an explanation of his failure to show any significant difference in cardiac output in the 3 modes studied.

Atrial synchronisation was shown to give a statistically significant improvement over ventricular pacing ($P > 0·05$) in these 8 patients (Sutton and Perrins, 1979).

Discussion

This paper has presented an explanation of available pacing systems illustrating their functional simplicity by means of block diagrams. Indications and contraindications to each system have been given, but in some aspects there remains controversy (Table 3).

Table 3 *Indications and contraindications for available and advanced pacemaker systems*

Pacer	*Indications*	*Contraindications*
AOO	Severe sinus bradycardia without physiological rate increase	Atrial paralysis High atrial threshold More rapid atrial rates resulting in competitive stimulation
VOO	Atrioventricular block with pacemaker dependence	Intermittent atrioventricular block Ventricular extrasystoles
AAI/AAT	Sick sinus syndrome with or without retrograde atrioventricular conduction	Atrial paralysis High atrial threshold Sick sinus syndrome with His-Purkinje disease (atrioventricular block)
VVI/VVT	Atrioventricular block with atrial fibrillation Sick sinus syndrome without retrograde conduction Sick sinus syndrome with atrial fibrillation Sick sinus syndrome with no haemodynamic benefit of atrial pacing	Poor haemodynamic response to VVI or VVT because of induced atrioventricular dissociation
VAT • $VD\frac{T}{I}$	Atrioventricular block with normal sinus node function	Atrioventricular block with abnormal sinus node function Atrioventricular block with atrial fibrillation
DVI	Atrioventricular block with abnormal sinus node function Sick sinus syndrome with atrioventricular block	Atrioventricular block or sick sinus syndrome with atrial fibrillation
$DD\frac{TI}{I}$	Atrioventricular block with abnormal sinus node function Sick sinus syndrome with atrioventricular block Atrioventricular block with normal sinus node function	Atrioventricular block or sick sinus syndrome with atrial fibrillation

Definition of symbols is given in the text.

Therefore, the actual clinical use in one pacemaker centre has been cited.

Choice of atrial or ventricular pacing in sick sinus syndrome is one area of controversy. This paper has shown that electrophysiological and haemodynamic considerations are necessary in making this choice. Haemodynamic benefit is usually available to the patient by using atrial or atrioventricular pacing; however, at present there is no available means of synchronising atrial stimulation rate with the body's needs so as to increase the pacing rate on exercise, for instance. This should produce greater haemodynamic benefit. Ventricular pacing can have undesirable effects by inducing retrograde atrioventricular conduction. Despite the fact that these two problems favour atrial pacing, this mode remains contraindicated in atrial fibrillation and atrial paralysis and when there is significant His-Purkinje system disease.

The onset of atrial fibrillation in the sick sinus syndrome has been shown to improve symptoms and especially to avert syncopal episodes (Vera *et al.*, 1977). Our patients with atrial fibrillation were all new cases who presented because of syncopal episodes despite the rhythm, so atrial fibrillation is not a panacea for syncope in this syndrome. Adoption of atrial pacing has been hindered by the expectation that atrioventricular block would develop in the foreseeable future, necessitating a premature change in the pacemaker system. Available data in comparatively large series of permanent atrial pacing, however, point against this (Kleinert *et al.*, 1977; Citron *et al.*, 1978; Greenberg *et al.*, 1978). Despite the fact that the majority of these patients did not undergo detailed electrophysiological study before the choice of atrial pacing (Kleinert *et al.*, 1977; Citron *et al.*, 1978), it appears that valuable guidance may be gained about the possible future development of atrioventricular block (Narula, 1971; Rosen *et al.*, 1971). Other contraindications to atrial pacing have been seen in this series whose small size may not therefore show the true incidence of high atrial threshold and the presentation of sick sinus syndrome with syncope caused by sinuatrial block but intrinsically fast sinus rate at other times (one case of each here). These two conditions are further contraindications to atrial pacing. At present, approximately one-third of patients with sick sinus syndrome will be suitable for atrial pacing. With increased availability of DVI and more advanced pacemakers which offer sensing and pacing in both atrium and ventricle (Fig. 12), all patients can receive atrial as well as ventricular leads except when atrial fibrillation, atrial paralysis, or high atrial threshold exists. When atrial stimulation is followed by a normal or a stimulated ventricular complex, retrograde atrioventricular conduction is minimised. It may be necessary to keep the PR interval short to prevent re-entry mechanisms (Fields *et al.*, 1973). Use of dual chamber pacemakers allays anxiety about the onset of atrioventricular block with atrial pacing.

Atrial pacing may have two further advantages in suitable patients. The incidence of escape tachycardias may be reduced or abolished even without the use of antiarrhythmic drugs and there may be a reduced rate of systemic embolism which has been claimed to be high, both without pacing and with ventricular pacing (*British Medical Journal*, 1973).

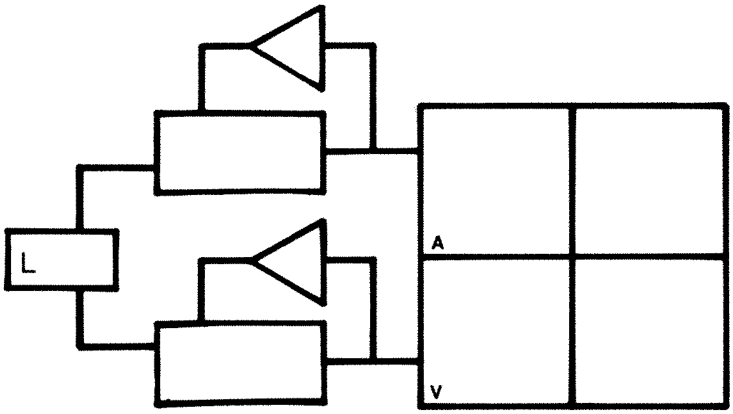

Fig. 12 *Advanced pacemaker DDT* $\frac{TI}{I}$ *which senses and paces in both atrium and ventricle, the co-ordination by means of a logic circuit L. (A) atrium, (V) ventricle.*

The indications for addition of atrial synchrony to ventricular pacing in atrioventricular block remain unclear. The lack of clarity has been dominated by difficulties with endocardial atrial leads often necessitating epicardial lead placement and by the relatively short life characteristics of early atrial synchronous pacemakers. A more encouraging report has recently been made by Carlens *et al.* (1977) using epicardial atrial lead placement by mediastinoscopy. This technique has not, however, achieved wide acceptance. For atrial synchronous ventricular pacing to achieve wide application, a satisfactory all endocardial lead system is necessary. Reports of large series using atrial leads with passive fixation mechanisms (Kleinert *et al.*, 1977; Greenberg *et al.*, 1978) indicate that this is now possible. With modern low current drain circuits, atrial synchronous pacemakers can be expected to exhibit much better life characteristics. Now the chief determinant of life will be the proportion of time during which the ventricles are driven at higher rates than 70 ppm. In this context a fresh review of patients presenting with atrioventricular block is justified.

Studies of sinuatrial node function by Holter monitoring, exercise stress test, and sinus node recovery time in patients with atrioventricular block in this series have shown a high incidence of abnormal sinus node function. There has also been a high incidence of intermittent or permanent atrial fibrillation. Both of these conditions are contraindications to atrial synchronous pacing. In 3 patients, prepacing studies were contraindicated because of frailty or complicating conditions. Thus atrial synchronous pacing was also contraindicated. One patient showed complete anterograde atrioventricular block but retrograde atrioventricular conduction was preserved. This may lead to atrial synchronous pacemaker-induced tachycardias (Castellanos *et al.*, 1968). In total, 28 (74%) patients were unsuitable for atrial synchronous pacemakers; however, the 15 with abnormal sinus node function and the patient with retrograde atrioventricular conduction should now be considered for DVI atrioventricular sequential pacemakers. Two patients with normal sinus node function had rare syncopal episodes, and atrioventricular block was not induced on exercise. Atrial synchronous pacemakers were not considered an advantage in these cases and ventricular demand VVI pacemakers were implanted.

The high incidence of abnormal sinus node function in patients with atrioventricular block was unexpected but is considered to be a manifestation of conduction tissue disease occurring throughout the heart. Atrial fibrillation is often the final rhythm in patients with sick sinus syndrome (Vera *et al.*, 1977) and atrial fibrillation may be seen to develop during the course of ventricular pacing for atrioventricular block. Shaw and Eraut (1970) have indicated that atrial fibrillation in atrioventricular block patients carries a poor prognosis. It is possible to postulate that many patients with atrioventricular block develop abnormal sinus node function and evolve towards atrial fibrillation as their conduction tissue disease increases. When an atrial synchronous pacemaker is replaced it is suggested that sinus node function is reassessed because atrioventricular sequential pacemaker DVI may have become more appropriate. Rapid technological development has resulted in the need for modification to the Parsonnet *et al.* (1974) classification of pacemakers. We propose that the third letter, which applies to the chamber used for sensing or triggering, be fractionated so that the activity of the atrium in this respect becomes the numerator and the ventricle the denominator. In some cases it may be necessary to indicate that both inhibition and triggering occur from the atrium such as in an advanced pacemaker which senses and paces in the atrium but also acts as an atrial triggered (synchronous) unit. The pacemaker in Fig. 12 should be represented by the symbols $\mathrm{DD}\frac{\mathrm{TI}}{\mathrm{I}}$ according to our proposed modification of the Parsonnet recommendations.

Conclusions

Sick sinus syndrome and atrioventricular block represent ends of a spectrum of conduction tissue disease with considerable overlap between them. Sick sinus syndrome represents 37 per cent of patients presenting for permanent pacing with either syncope or heart failure. With the advent of an electrode yielding satisfactory endocardial sensing and pacing, a need is created for electrophysiological and haemodynamic studies to determine the optimal pacing system for each patient. In the future some patients now given ventricular pacing and atrioventricular sequential pacing will benefit from an advanced type of pacemaker which senses and paces both atrium and ventricle.

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Cardiomyopathic syndrome caused by coronary artery disease

III: Prospective clinicopathological study of its prevalence among patients with clinically unexplained chronic heart failure[1]

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SUMMARY Each day, for one year, the medical records of adult patients who died in hospital were reviewed before seeing the necropsy findings. For those patients who had had chronic left or left and right heart failure, a presumptive cause was assigned on the basis of antemortem clinical data. Of 740 consecutive patients who were studied at necropsy, 90 had had chronic heart failure. In 15 patients the cause of heart failure was not apparent by clinical criteria; of these, 7 were found at necropsy to have cardiomyopathic syndrome caused by coronary artery disease. In retrospect, the presence of overt diabetes mellitus was a clue that cardiomyopathy caused by coronary artery disease was the cause of clinically unexplained heart failure; 5 of 7 patients with unexplained heart failure who were found to have this at necropsy were diabetic, whereas only 1 of the other 8 patients with clinically unexplained heart failure was diabetic ($P < 0.05$). Patients in whom clinically unexplained heart failure was found to be the result of cardiomyopathy caused by coronary artery disease had multiple myocardial infarctions on pathological examination, which, with one exception, were nontransmural. By contrast, myocardial infarctions were transmural on pathological examination in each of 7 matched 'controls' with heart failure, in whom the diagnosis of coronary artery disease had been clinically apparent ($P < 0.01$).

Cardiomyopathic syndrome caused by coronary artery disease is far more common than are the other clinicophysiological syndromes caused by coronary artery disease that are associated with chronic heart failure (ventricular aneurysm; relatively isolated mitral regurgitation; ventricular septal rupture; and transient recurrent ischaemia) (Brody and Criley, 1970; Baxley *et al.*, 1971; Yatteau *et al.*, 1974; Dash *et al.*, 1977b; Lee *et al.*, 1977). Furthermore, the other syndromes of coronary artery disease that cause heart failure, when they occur, are almost always considered as diagnostic possibilities in an individual patient with heart failure because of an accompanying history of chest pain, because of the detection of a cardiac murmur, or because of electrocardiographic evidence of myocardial infarction. By contrast, cardiomyopathy caused by coronary artery disease is known to occur, at least occasionally, without accompanying clinical clues to the presence of coronary artery disease (Raftery *et al.*, 1969).

Why the diagnosis of cardiomyopathy caused by coronary artery disease should not ever be inapparent on clinical grounds is unclear, since the mechanism of heart failure in such patients is a substantial reduction in left ventricular ejection fraction brought about by multiple myocardial infarctions (Yatteau *et al.*, 1974; Dash *et al.*, 1977b). In addition, the frequency with which cardiomyopathic syndrome caused by coronary artery disease is an unsuspected cause of heart failure is not established. The results of catheterisation studies suggest that cardiomyopathy caused by coronary artery disease is only

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rarely an unsuspected diagnosis (Yatteau *et al.*, 1974; Dash *et al.*, 1977b). Patients undergoing catheterisation, however, represent a selected population. The possibility remains that among elderly patients who would often not be candidates for catheterisation because of age considerations, cardiomyopathy caused by coronary artery disease may often not be accompanied by clinical stigmata of underlying coronary artery disease.

The present study is a prospective clinicopathological analysis of the prevalence of cardiomyopathy caused by coronary artery disease among patients whose heart failure is unexplained on clinical grounds, but who are not considered to be candidates for cardiac catheterisation by the physicians caring for them. In addition, we examine whether a pathological explanation exists for the absence of clinical stigmata of coronary artery disease in patients in whom cardiomyopathy caused by coronary artery disease is found to be the cause of clinically unexplained heart failure. Finally, because we have found cardiomyopathy caused by coronary artery disease to be particularly common among diabetic patients with coronary artery disease (Dash *et al.*, 1977a), we ask whether the presence of diabetes mellitus is a clinical clue that cardiomyopathy caused by coronary artery disease is the cause of heart failure when other clues suggesting the presence of coronary artery disease are absent.

Methods

CLINICAL CLASSIFICATION

The medical records of all patients more than 20 years of age who died in hospital and who came to necropsy were reviewed each day, during a 1-year period (1 October 1974 to 30 September 1975). Based on antemortem clinical data, patients who had had chronic heart failure were identified, and a presumptive cause of heart failure was specified, either before necropsy or before knowledge of the cardiac findings at necropsy.

Patients were identified as having had chronic left heart failure if all of the following had been present some time in their course (not necessarily concurrently): (1) dyspnoea; (2) digitalis and diuretic therapy; (3) apical third heart sound; (4) basilar râles; and (5) pulmonary venous hypertension (upper zone flow redistribution, with or without interstitial or alveolar pulmonary oedema) on a chest *x*-ray film report. Clinical evidence of right heart failure was not required. Only patients who had had chronic heart failure before the terminal hospital admission were included. Patients who had had only a single episode of heart failure in the setting of an acute event, such as acute myocardial infarction, were excluded.

Patients identified as having had chronic left heart failure were assigned a presumptive diagnosis of coronary artery disease, valvular heart disease, congenital heart disease, cardiomyopathy (unrelated to coronary artery disease), heart failure resulting from hypertension, or unexplained heart failure. Coronary artery disease was assigned when either a history of typical angina pectoris, a history of myocardial infarction, or a transmural myocardial infarction pattern on the electrocardiogram had been present. Valvular or congenital heart disease was assigned when catheterisation evidence was available or if the clinical diagnosis had been made by an experienced clinical cardiologist. Cardiomyopathy (unrelated to coronary artery disease) was assigned when normal or insignificantly diseased coronary arteries and the absence of important valvular disease had been proved by catheterisation. All other patients were classified as having unexplained heart failure. For purposes of this study, hypertension was not considered to be a cause of chronic heart failure unless severe uncontrolled hypertension was present at the time that heart failure was present.

Documentation in the medical record of blood glucose levels was erratic, so diabetes mellitus was defined when the diagnosis had been made during life by the patient's doctor and this had required dietary or drug treatment, or both. A history of hypertension was defined as a blood pressure recording of greater than 140/90 mmHg on 2 separate occasions.

NECROPSY ANALYSIS

In addition to routine necropsy examination, postmorten coronary angiography (Schlesinger, 1938) was performed in 12 of 15 patients in whom heart failure had been unexplained. In each of these cases, the extramural coronary arteries were removed from the heart. After complete formalin fixation and decalcification, each artery was cross-sectioned at 2 mm intervals, and the degree of stenosis in each segment was recorded. Coronary artery disease was judged to be present when 70 per cent or greater reduction in cross-sectional luminal area was present.

In all patients classified as having had unexplained heart failure, the ventricular myocardium was examined by gross inspection of transverse ventricular sections and by histological evaluation of samples from both randomly selected and pathological areas. Transmural infarction was defined as the presence of dense, contiguous fibrosis extending from the endocardium to the epicardium. Non-transmural infarction was defined as being present when either confluent fibrosis or dense patches of fibrosis occupied at least one-half of a low-power microscopical field, but did not extend contiguously from the endocardium to the epicardium. Stains for amyloid were not routinely performed.

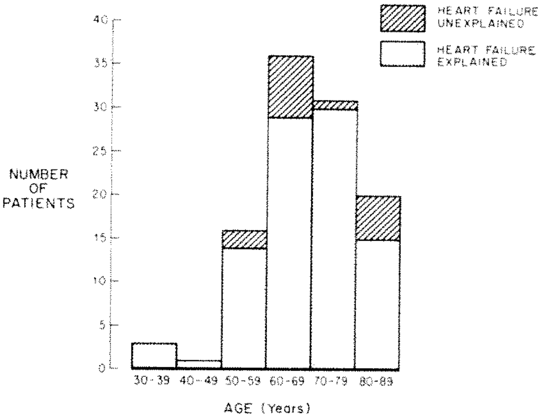

Fig. *Histogram of the age distribution of the 90 study patients who had had clinical evidence for chronic heart failure. Within each decade, the subgroup of patients with clinically unexplained heart failure is shown by the shaded portion of the bar.*

CASE CONTROL COMPARISON

Patients who had been classified as having unexplained heart failure and who were discovered at necropsy to have coronary artery disease as its cause ('case') were randomly and individually matched for sex and, as closely as possible, for age to patients who had been classified before necropsy as having coronary artery disease as the cause of chronic left heart failure (control). The pathological findings in the coronary circulation and in the myocardium were compared in the two groups. The pathologist (JTF) who examined each heart and coronary circulation did not know whether the case being examined was a 'case' or a control.

STATISTICAL ANALYSIS

Proportions of groups having the same event were compared by Fisher's exact test.

Results

During the 1-year period, necropsy was performed in 740 patients who died in hospital. Of these patients, 90 had had, by our criteria, chronic left heart failure. Their age distribution is shown in the Fig. Thirty-six patients (40%) were 75 or older, and only 4 patients (4%) were less than 50 years old. The clinical classification of the presumptive causes of left heart failure is shown in Table 1. Heart failure was not attributed to hypertension in any of the patients. Of the 75 patients who had been assigned coronary artery disease, valvular heart disease, congenital heart disease, or cardiomyopathy (unrelated to coronary artery disease) as the presumptive cause of heart failure, the diagnosis was confirmed as correct at necropsy in 69. Of the 6 patients in whom the clinical diagnosis was unconfirmed, none had undergone cardiac catheterisation. Thus, the clinical diagnosis was correct in 86 per cent (36 of 42) of patients not catheterised in whom the cause of heart failure had been thought to be diagnosable on clinical grounds. Of the 6 patients in whom the clinical cardiac diagnosis was mistaken, 2 had insufficient findings at necropsy to account for heart failure.

Necropsy findings and clinical features of the 15 patients classified clinically as having unexplained heart failure are shown in Table 2: 7 were found to have coronary artery disease as the cause of their heart failure, which occurred in the form of cardiomyopathy caused by coronary artery disease (multiple areas of infarction) in all 7; 5 had cardiomyopathy unrelated to coronary artery disease; and

Table 1 *Presumptive clinical diagnosis of causes of left heart failure*

Presumptive clinical diagnosis	*Total no. of patients*	*No. of patients in whom diagnosis not documented by cardiac catheterisation during life*	*No. of patients in whom clinical diagnosis not confirmed by necropsy findings*
Coronary artery disease	23	21	3
Valvular heart disease	48 (15)*	21	3
Congenital heart disease	1	0	0
Cardiomyopathy (unrelated to coronary artery disease)	3	0	0
Total	75	42	6
Unexplained	15	15	—

*The number in parentheses refers to patients in whom the clinical events suggested that coronary artery disease was present in addition to valvular heart disease.

Table 2 *Patients who on clinical grounds were assigned 'unexplained' as cause of chronic left heart failure*

Case no.	*Age, sex*	*Electrocardiogram*	*Diabetes*	*Hypertension*	*Heart weight (g)*	*CAD*†	*LV chamber dilatation*‡	*LV wall*§ *thickness (cm)*	*Cause of heart failure at necropsy*
1*	60, F	Complete heart block	Yes	Yes	369	3	3+	1·5	CM-CAD**
2*	87, M	Intraventricular conduction defect	No	No	536	3	4+	1·5	CM-CAD
3*	55, F	Poor praecordial R wave progression	Yes	No	405	3	2+	1·3	CM-CAD
4*	86, M	Non-specific ST-T abnormalities	Yes	No	456	2	1+	1·6	CM-CAD¶
5*	65, M	Left ventricular hypertrophy	Yes	No	354	3	3+	1·0	CM-CAD
6*	74, M	Left ventricular hypertrophy	No	Yes	553	3	2+	2·0	CM-CAD
7	81, M	Non-specific ST-T abnormalities	Yes	No	340	2	1+	1·7	CM-CAD
8*	58, M	Poor praecordial R wave progression	No	No	663	0	3+	1·4	Cardiomyopathy
9	64, M	Intraventricular conduction defect	No	Yes	660	0	4+	2·3	Cardiomyopathy
10*	62, F	Complete heart block	No	Yes	483	0	2+	1·8	Cardiomyopathy
11*	84, F	Intraventricular conduction defect	Yes	Yes	548	0	2+	1·6	Cardiomyopathy
12*	66, F	Intraventricular conduction defect	No	No	568	0	3+	1·3	Cardiomyopathy
13*	62, M	Poor praecordial R wave progression	No	No	498	1	3+	2·1	Calcific aortic stenosis
14	82, F	Left ventricular hypertrophy	No	Yes	500	1	1+	1·7	Calcific aortic stenosis
15*	60, M	Left ventricular hypertrophy	No	No	619	2	3+	1·2	Rheumatic valvular disease, aortic, mitral, and tricuspid

*Postmortem selective coronary angiography performed.
†Coronary artery disease (number of vessels with 70% or greater stenosis).
‡Left ventricular chamber dimensions, judged subjectively, 0-4+.
§Measured in mid anterior wall.
¶Rheumatic valvular disease, aortic and mitral, was also present.
**CM-CAD, cardiomyopathic syndrome caused by coronary artery disease.

3 had significant valvular heart disease, the importance of which had been unappreciated during life. A history of hypertension was present in 6 patients, but heart failure was not attributed to hypertension in these patients (see Methods section). The data in Table 2 imply that only a single cause of heart failure was found in each patient. In fact, multiple cardiac abnormalities (excluding a history of hypertension as an abnormality) were present in 4 patients. But only in 1 patient—a patient with cardiomyopathy caused by coronary artery disease and rheumatic valvular disease—did more than one abnormality appear potentially related to heart failure (and the valvular abnormalities were relatively minor in this patient). All 3 patients with severe valvular disease also had coronary artery disease, but the heart failure was judged to be unrelated to coronary artery disease (only 1 of the 3 had myocardial infarction, and in that patient the infarct was small). We have assumed that abnormalities of the heart valves or myocardium that are present on a microscopical basis only, that is that do not cause an abnormality apparent on gross examination of the valves or myocardium (such as post-inflammatory or degenerative changes or microscopic amyloid), are not severe enough to cause chronic heart failure.

Six of the patients classified clinically as having had unexplained heart failure had been diabetic (4 on oral antidiabetic agents, 2 on insulin; adult onset in 5). Of these, 5 were in the group of 7 patients who had coronary artery disease discovered at necropsy to be the cause of heart failure, and only 1 was in the group of 8 patients who were found to have a cause of heart failure other than coronary artery disease ($P < 0{\cdot}05$) (Table 2). Hypertension, however, was not a marker of whether coronary artery disease was found at necropsy in patients who had been classified as unexplained heart failure. Of 6 patients who had been hypertensive, 2 were found at necropsy to have coronary artery disease and 4 were not.

A comparison is shown in Table 3 of the extent of coronary artery disease and of the type and distribution of myocardial infarction in patients who had been classified as having unexplained heart failure, but in whom coronary artery disease was found at necropsy to have been the cause of heart failure ('cases'), and 'control' patients who had been given a

Table 3 *Comparison of extent of coronary artery disease and of type and distribution of myocardial infarctions found at necropsy in patients with clinically unexplained heart failure found to have cardiomyopathy caused by coronary artery disease ('cases') and in 'control' patients (matched for age and sex) who had been classified as having coronary artery disease as presumptive cause of heart failure on clinical grounds*

	Age	*LCA*† *stenosis*	*No. of diseased vessels*‡	*No. of sites of remote infarction (fibrosis)*§		*Number of sites of recent infarction*§	*Syndrome of coronary artery disease that caused heart failure*
				Non-transmural	*Transmural*		
'Cases'							
1	60	Yes	3	2	0	1	CM-CAD*
2	87	No	3	2	0	0	CM-CAD
3	55	Yes	3	3	0	1	CM-CAD
4	86	No	2	2	0	1	CM-CAD
5	65	No	3	3	0	1	CM-CAD
6	74	Yes	3	2	0	1	CM-CAD
7	81	No	2	1	1	1	CM-CAD
'Controls'							
1	61	Yes	3	1	1	0	CM-CAD
2	87	No	3	2	1	0	CM-CAD
3	55	No	3	1	1	0	CM-CAD
4	81	No	2	2	2	0	CM-CAD
5	50	Yes	3	2	1	1	CM-CAD
6	74	No	1	0	1	0	LV¶ aneurysm
7	75	No	3	1	2	0	CM-CAD

*CM-CAD, cardiomyopathy caused by coronary artery disease.
†LCA, main left coronary artery.
‡Other than LCA.
§Number of 4 left ventricular sites (free anterior wall, septum, posterior wall, lateral wall) showing infarction.
¶LV, left ventricular.

presumptive clinical diagnosis of coronary artery disease. The 2 groups differed in the frequency with which remote infarction was transmural as compared with non-transmural. Of the 7 'cases', only 1 had a transmural infarction, which was posterolateral in location, whereas each of the 7 'controls' had transmural infarctions ($P < 0{\cdot}01$), which involved the anterior left ventricular wall in all.

Discussion

The present study was carried out prospectively so that our judgement as to the probable cause of heart failure would be made, as it is in everyday clinical practice, on the basis of clinical information alone and so that postmortem coronary angiography could be performed in cases where the cause of heart failure was not apparent. Our experience, similar to that of others (Crawford, 1977), is that routine examination of the coronary arteries at necropsy, as compared with postmortem coronary injection studies, results in an appreciable underdiagnosis of coronary artery disease. Our study has the disadvantages of necessarily limited numbers of patients and of sharing with all necropsy studies the fact that it is not necessarily applicable to living populations.

Even with these reservations, however, one conclusion of our study seems clear: cardiomyopathic syndrome resulting from coronary artery disease which is not apparent from the patient's history and the electrocardiogram is a more frequent cause of clinically unexplained chronic heart failure than the results of cardiac catheterisation studies suggest (Yatteau *et al.*, 1974; Dash *et al.*, 1977b). In 17 per cent of our necropsied patients, chronic left heart failure could not be explained clinically. In approximately one-half of such patients, necropsy showed that there was cardiomyopathy caused by coronary artery disease. Looking at the issue from another standpoint, of a total of 25 patients in whom coronary artery disease was the cause of chronic heart failure (excluding 2 patients who had undergone cardiac catheterisation during life), the diagnosis of coronary artery disease had not been apparent in 7 (28%). Twenty-eight per cent may be considered the frequency with which a *false negative* diagnosis of coronary artery disease as the cause of chronic heart failure was made in our study. By comparison, the diagnosis of coronary artery disease was *false positive* in 14 per cent of cases; of 21 patients who had not undergone cardiac catheterisation and in whom heart failure was attributed on clinical grounds to coronary artery disease, the diagnosis was found to be incorrect in 3.

The relatively high prevalence of false negatives in the diagnosis of cardiomyopathy caused by coronary artery disease does not imply that a more extensive diagnostic evaluation is required in caring for the individual patient with unexplained heart failure.

No convincing data exist to suggest that the management of patients with cardiomyopathy caused by coronary artery disease should differ from the management of patients with dilated cardiomyopathy of the idiopathic type (Yatteau *et al.*, 1974; Wexler *et al.*, 1976; Dash *et al.*, 1977b).

Rose and Wilson (1959) found a lower prevalence of coronary artery disease in their study of necropsied patients with clinically unexplained heart failure than we have, but they utilised standard necropsy techniques for the identification of coronary artery disease, which probably underestimate its prevalence. Furthermore, several of their patients appear to have been misidentified as having had heart failure, since 36 per cent were found not to have specifiable heart disease at necropsy. It is important to use criteria for heart failure that, in combination and including radiological signs, are highly specific (Harlan *et al.*, 1977), though undersensitive, in its detection. Consequently, we failed to find cardiac findings sufficient to explain the occurrence of heart failure in only 2 of 90 patients in our study.

Pomerance has found that 65 per cent of patients with heart failure who are over 75 years of age have multiple cardiac abnormalities (Pomerance, 1965a). In the present study, we seldom found it necessary to assume more than one cause of heart failure in an individual patient, either on clinical grounds or after necropsy, perhaps because 60 per cent of our patients were less than 75 years of age. Hypertension was not assumed in our study to be a cause of heart failure unless sustained severe hypertension was present at the time that heart failure was present (see below), whereas past hypertension was included as a causal factor for heart failure in the Pomerance study. Moreover, we have, by design, specified as the cause of heart failure the predominant cardiac abnormality present, and have reported more than one cause only if a second abnormality appeared likely to have been of haemodynamic significance. Hence, our study possibly underestimates the number of patients in whom heart failure is the result of a combination of abnormalities, perhaps, in some cases, no one of which would have caused heart failure in itself. For the same reasons, we may have also underestimated the contribution of mitral annular calcification as a cause of heart failure (Pomerance, 1970). We found mitral annular calcification to be the predominant cause of heart failure in only one patient. Even so, we believe that chronic heart failure is most often the result of a single factor, and this is seldom mitral annular calcification, even though multiple cardiac abnormalities, including mitral annular calcification, are frequently present in the most elderly. In those patients who are of principal interest in the present study, namely, those in whom a cause of heart failure was not apparent clinically, a single cause was found at necropsy in 14 of 15.

One-third of the patients in our study in whom heart failure was unexplained clinically were found at necropsy to have cardiomyopathy. The hearts of such patients were strikingly increased in weight, and showed left ventricular chamber dilatation that was of at least moderate degree in each and was of extreme degree in 3; no important valvular abnormalities or coronary artery lesions were present. The gross pathological findings correspond to those of idiopathic congestive cardiomyopathy (Roberts and Ferrans, 1975), at least in the 3 cases in which the most striking degree of left ventricular chamber dilatation was present. We have assumed that hypertension is not the predominant cause of chronic heart failure unless hypertension is not treated or cannot be controlled with medical treatment. This is because effective antihypertensive therapy greatly reduces the number of patients with recurrent episodes of heart failure as well as the number in whom heart failure is the cause of death among patients with hypertension (Wolff and Lindeman, 1966; Hodge and Smirk, 1967; Veterans Administration Cooperative Study Group on Antihypertensive Agents, 1970), at least during the first few years of follow-up. Therefore, heart failure was not attributed to hypertension in a single patient in our study, because in no patient was sustained, uncontrolled, severe hypertension present at the time that heart failure was present. Nevertheless, the possibility exists that an occasional patient with hypertension suffers the development of a 'hypertrophic cardiomyopathy' that, once present, persists to cause heart failure even after hypertension is controlled. If so, 3 of the 5 patients in whom clinically unexplained heart failure was ascribed after necropsy to cardiomyopathy should be considered candidates for the diagnosis of hypertension-induced cardiomyopathy, because they had a history of treated hypertension.

We found no instances in which chronic heart failure was attributable to senile cardiac amyloidosis, probably because most of our patients were less than 80 years of age, and senile cardiac amyloidosis only becomes common over the age of 80 (Pomerance, 1965b). Though we performed no special stains for amyloid, we believe that we were unlikely to have overlooked cases in which senile cardiac amyloid was responsible for heart failure, because amyloid deposition is severe and apparent on gross examination in cases in which it causes heart failure (Pomerance, 1965b).

Studies of patients undergoing cardiac catheterisation have shown that cardiomyopathy caused by coronary artery disease is the result of mutiple myocardial infarctions, and, furthermore, that the infarctions are distributed in the territory of more than one coronary artery (Yatteau *et al.*, 1974; Dash *et al.*, 1977b). The patients with cardiomyopathy caused by coronary artery disease in the present study in whom heart failure had been unexplained during life had similar findings, by necropsy criteria, to patients who have been identified in catheterisation studies: multiple infarctions and multivessel coronary artery disease. But an explanation as to why the diagnosis of cardiomyopathy caused by coronary artery disease had not been apparent, at least on the electrocardiogram, was forthcoming: the remote infarctions found at necropsy were either nontransmural in location, and hence not diagnosable by electrocardiographic Q waves (Georas *et al.*, 1963), or were transmural but located in areas where transmural infarctions are unassociated with Q waves in the standard 12-lead electrocardiogram. Why typical ischaemic cardiac pain was absent in these patients is unclear. Approximately 25 per cent of patients who suffer a transmural myocardial infarction do not experience typical chest pain (Kannel *et al.*, 1970). The present study shows that nontransmural myocardial infarctions also, even when multiple, may occur without typical chest pain.

This study also suggests that the presence of clinically overt diabetes mellitus appears to be a useful clue to the diagnosis of cardiomyopathy caused by coronary artery disease in patients whose chronic heart failure would otherwise be unexplained. Unexplained heart failure was caused by cardiomyopathy resulting from coronary artery disease in 83 per cent of patients who were being treated for diabetes, but the same was true of only 22 per cent of patients who were not being treated for diabetes. Though the number of patients studied is small, the difference is significant. This simple observation is interesting and somewhat surprising in view of the uncertainty that is extant with regard to the definition of diabetes, at least on the basis of the glucose tolerance test, in this age group (Andres, 1971). The increased prevalence of undiagnosed cardiomyopathy caused by coronary artery disease in diabetics is almost certainly the explanation for the excessive prevalence of heart failure, compared with the prevalence of overt coronary events, in the diabetic population of the Framingham study (Kannel *et al.*, 1974). Perhaps cardiomyopathy caused by coronary artery disease is a more frequent cause of otherwise unexplained heart failure in diabetics because diabetics are more prone to myocardial infarctions that are painless. To our knowledge, however, a definite relation between diabetes mellitus and 'silent' myocardial infarction has never been conclusively shown (Kannel *et al.*, 1970).

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British Heart Journal, 1979, **41**, 621-623

Marfanoid hypermobility syndrome associated with coarctation of the aorta

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SUMMARY There are intimate interrelations between various elements of connective tissue, viz. collagen, elastin, and glycoproteins. It is not unexpected that Marfan and Ehlers-Danlos syndromes share common features. The condition is labelled as Marfanoid hypermobility syndrome. In the patient described here, the Marfanoid hypermobility syndrome was associated with coarctation of the aorta which was corrected surgically.

Ehlers-Danlos syndrome is characterised by hypermobility of joints, hyperextensibility of skin, defective healing, and easy bruising (McKusick, 1972a), while the usual features of the Marfan syndrome are long limbs, arachnodactyly, a high arched palate, and skeletal deformity, particularly spinal scoliosis and pectus excavatum. Ectopia lentis is present in 70 per cent of patients with Marfan's syndrome but the skin is normal except for the common presence of striae (McKusick, 1972b).

Because there are intimate interrelations between various elements of connective tissue, i.e. collagen, elastin, and glycoproteins, it is not unexpected that Marfan and Ehlers-Danlos syndromes, two inherited connective disorders, may share common features. Walker *et al.* (1969) described a patient whose body habitus was typical of the Marfan syndrome but who also had the gross joint hypermobility and cutaneous hyperextensibility of the Ehlers-Danlos syndrome and these authors labelled the condition as 'Marfanoid hypermobility syndrome'. Cotton and Brandt (1976) have described two cases of Marfanoid hypermobility syndrome, one associated with 'floppy' mitral valve and the other with cystic medionecrosis of the aorta. The unusual association of coarctation of the aorta and Marfanoid hypermobility syndrome, which was seen in the present case and has not been documented previously, has prompted the publication of this report.

Case report

A 15-year-old boy was admitted to the Pahlavi Hospital, Tabriz, Iran, with complaints of diplopia and blurring of vision of 4 months' duration. He also had praecordial pain, radiating to the left shoulder and back, pain in the calf muscles on both sides, and severe headache during exercise of the same duration. He gave a history of occasional episodes of epistaxis and difficult healing of wounds following injuries. There was no family history of dolichomorphism, eye disorders, bleeding, abnormal skin, defective wound healing, hypermobility of joints, or sudden death.

Examination disclosed a young boy of thin build with height of 172 cm and arm span of 178 cm. His upper: lower segment ratio was 0·92 (normal range 0·93 ± 0·08). His weight was 50·4 kg and blood pressure was 145/100 mmHg in both upper extremities in the erect and supine positions. Blood pressure in the lower extremities could not be recorded as the arterial pulsations in them were too feeble. There were pulsations of the carotid arteries in the neck and of collaterals over the back, adjacent to the scapulae. Murmurs were heard over these pulsating vessels. He had a high arched palate. His hands were narrow with thin elongated fingers.

His skin was hyperplastic (Fig. 1A) and epicanthal folds were present. The joints of the hands and feet

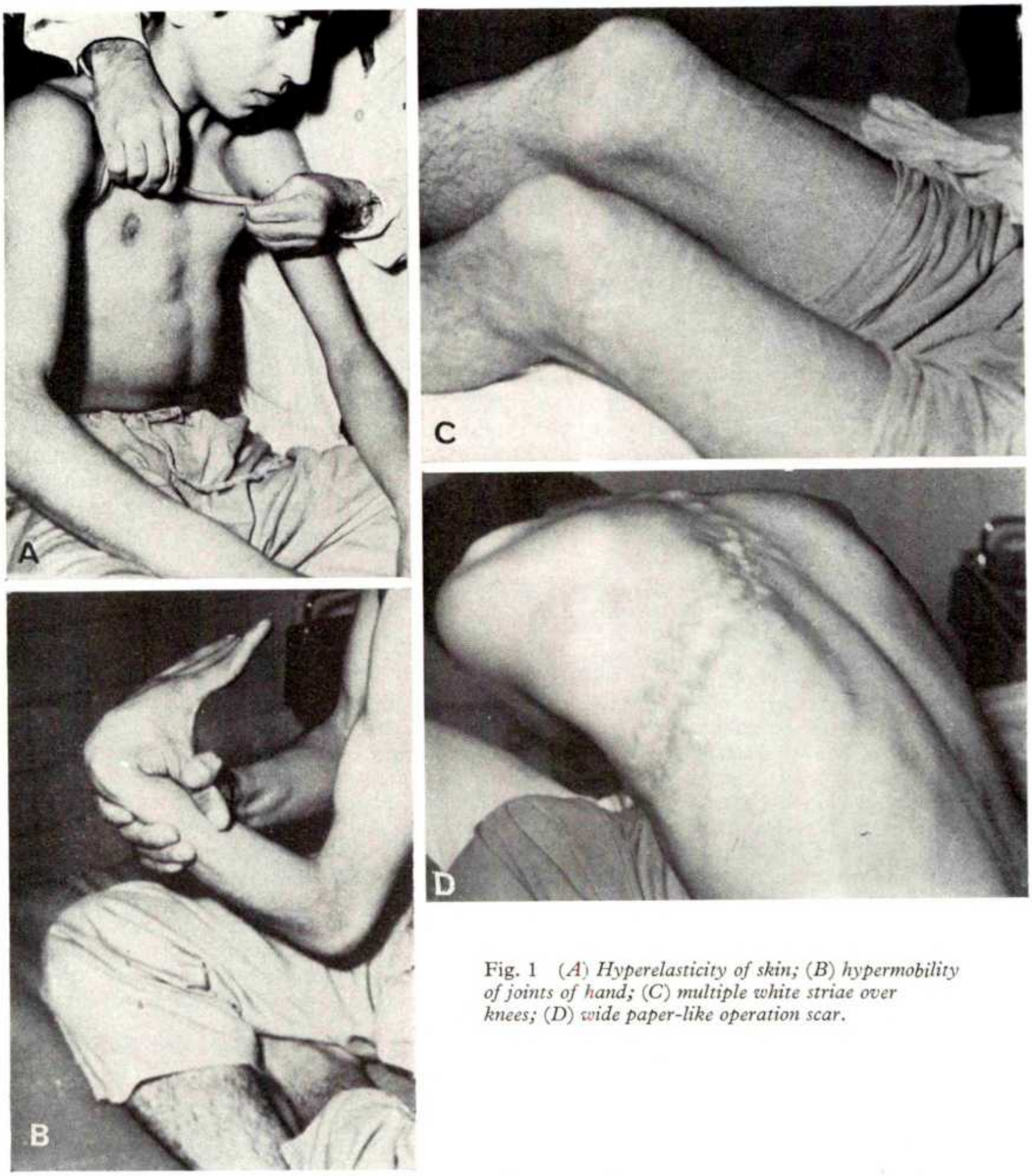

Fig. 1 (*A*) *Hyperelasticity of skin;* (*B*) *hypermobility of joints of hand;* (*C*) *multiple white striae over knees;* (*D*) *wide paper-like operation scar.*

could be hyperextended (Fig. 1B). The skin over the knee joints showed white striae (Fig. 1C). There were many cigarette paper scars of healed wounds over the body. There was no abnormality of the respiratory system. Ophthalmic examination was normal.

The patient's haemoglobin was 14 g/dl and coagulation studies of the blood were normal. The urinalysis and cytogenetic studies did not show any abnormality. The *x*-ray film of the chest showed notching of ribs, left ventricular hypertrophy, and a positive '3' sign.

He was operated on for coarctation of the aorta. There was distinct bleeding during the operation and haemostasis was obtained with difficulty. The stenosis was postductal. The stenotic portion

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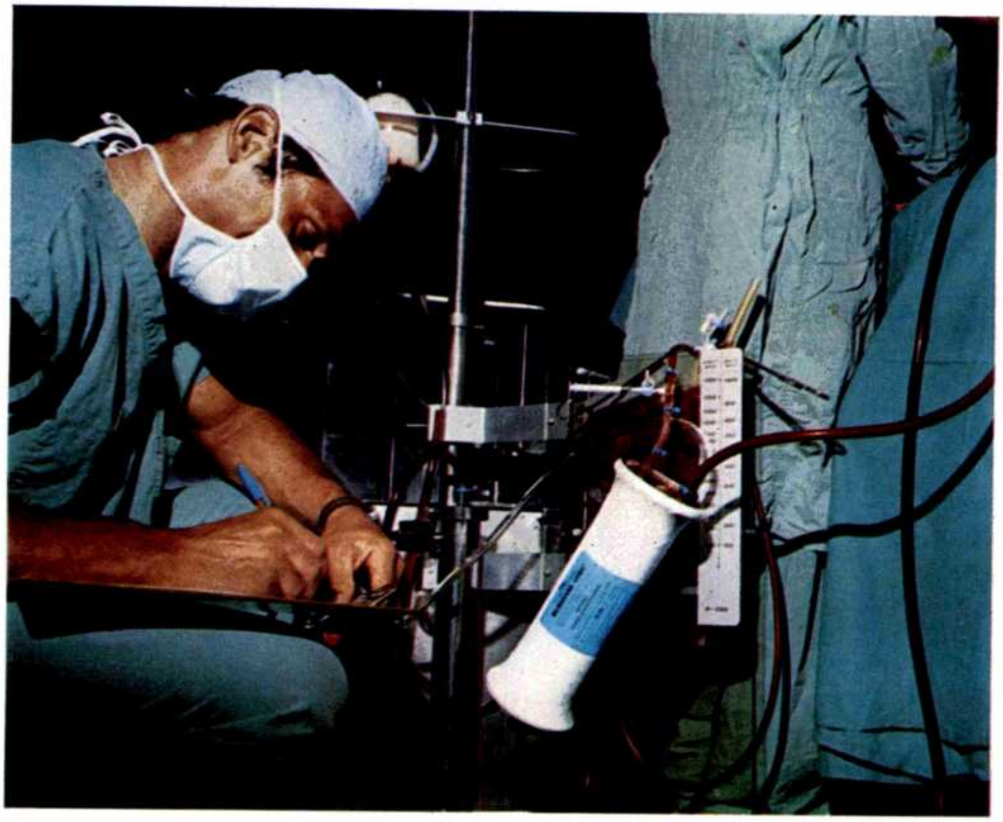

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was resected and replaced with 'dacron' graft. The postoperative course was uneventful. The wound healed with a wide paper-like scar (Fig. 1D). One month after operation his blood pressure was 120/85 mmHg in the upper extremities and 100/60 mmHg in the lower extremities, with good peripheral pulsations.

Discussion

Patients with features of both Marfan and Ehlers-Danlos syndromes have been reported in the literature (Goodman *et al.*, 1965; Walker *et al.*, 1969; Birkenstock *et al.*, 1973; Motoyoshi *et al.*, 1973; Cotton and Brandt, 1976) and these authors labelled this condition as a separate entity, the Marfanoid hypermobility syndrome. The hallmark of Marfan syndrome is dolichostenomelia. The cutaneous hyperextensibility and paper scars, the chief features of Ehlers-Danlos syndrome, are not usually present in Marfan's syndrome. The present case had arachnodactyly, high arch palate, and white skin striae, which are characteristic of the Marfan syndrome, and he also had hyperextensibility of the skin, paper scars, and hypermobility of the joints of the hand and feet, which are features of Ehlers-Danlos syndrome and, thus, he can be considered to be another example of the Marfanoid hypermobility syndrome. Cotton and Brandt (1976) have described cardiovascular abnormalities in 2 cases of Marfanoid hypermobility syndrome, one had 'floppy' mitral valve and the other presented with aortic aneurysm caused by cystic medionecrosis of the aorta. The present case had associated coarctation of the aorta which has not been described previously.

Ehlers-Danlos syndrome has been subdivided into 7 subgroups on the basis of clinical and genetic differences. A specific biochemical defect has been identified in 3 of these subgroups. The nature of the basic defect in Marfan's syndrome is not clear. Goodman *et al.* (1965) and Motoyoshi *et al.* (1973) found autosomal dominant transmission of both the Ehlers-Danlos and Marfan syndromes in several family members of a patient, with features of both Ehlers-Danlos and Marfan syndromes and have raised the possibility that the two conditions are inherited simultaneously. The lack of evidence of either the Ehlers-Danlos or Marfan syndrome in the relatives of the present patient and those reported by Walker *et al.* (1969) and Cotton and Brandt (1976) makes it unlikely that these patients inherited two generalised connective tissue disorders, and they appear to have resulted from a spontaneous mutation.

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Hypertrophic cardiomyopathy associated with sudden death during marathon racing

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SUMMARY An experienced marathon runner died suddenly during a competitive race. At necropsy, ventricular hypertrophy but no asymmetrical septal hypertrophy was found. Histological studies showed features of hypertrophic cardiomyopathy. The coronary arteries were normal. We propose that the runner died from myocardial ischaemia, precipitated by marathon running on a background of hypertrophic cardiomyopathy. Excess cardiac work, induced by marathon running in the presence of mild congenital cardiac defects, could have contributed to the development of the cardiomyopathy.

Necropsy reports on marathon runners are very uncommon. In 1961, Currens and White reported the necropsy findings of Clarence de Mar, the legendary American who had been a marathon runner for 50 years. A striking cardiovascular finding was the size of the coronary arteries which were estimated to be two to three times the normal diameter, and the paucity of coronary atherosclerosis. This finding has been cited as supportive evidence for the controversial hypothesis that marathon running influences coronary atherosclerosis (Bassler, 1977; Noakes *et al.*, 1977). Green *et al.* (1976) reported the case of a marathon runner who collapsed during a race, was resuscitated, but later died. At necropsy the clinical diagnosis of myocardial infarction was confirmed but the patient was found to have normal coronary arteries. The possible cause of this unusual combination was debated (*Annals of Internal Medicine*, 1976) but the possibility exists that marathon running can precipitate myocardial infarction in the presence of normal coronary arteries.

We here report the findings in a 42-year-old man who died suddenly during a marathon race. At necropsy a diagnosis of hypertrophic cardiomyopathy was made. Though the patient had normal coronary arteries, we cannot exclude that he died from myocardial ischaemia, precipitated by marathon running on a background of hypertrophic cardiomyopathy.

Case report

The deceased, a 42-year-old man, was found at the age of 7 to have a cardiac murmur and was advised to restrict his physical activity. This advice was apparently ignored because he excelled in competitive sport until the age of 27, when he consulted a cardiologist for firm advice about the safety of his continuing in competitive athletics. A diagnosis of ventricular septal defect was made and he was advised to undergo cardiac catheterisation but this was not done. An electrocardiogram was normal, but slight prominence of the right ventricular outflow tract was noted on screening of the heart.

In 1965, at the age of 32, he was seen at Groote Schuur Hospital by the late Professor V. Schrire. Interrogation revealed that a grandfather had died from a heart attack at the age of 42, that the patient's father had died suddenly shortly after exercise, and that one of his sons had suffered an attack of rheumatic fever. The patient was a 'moderate smoker', a habit which he subsequently stopped when he took up long distance running. On clinical examination, a grade 2-3/6 systolic murmur was heard, maximal in the 4th left interspace close to the sternum. The murmur did not radiate. As there were no other clinical findings, a diagnosis of a Roger type ventricular septal defect was made and this was considered to be of no haemodynamic significance.

In 1972, at the age of 39, he took up long distance running and in May 1973 he completed the 56 mile Comrades Marathon between Durban and Pietermaritzburg in 8½ hours. During that race he was troubled by dyspnoea and chest pain. A further attack of chest pain was precipitated by running after an emotional argument with an official.

For the following two years he continued to run regularly. In April 1974 he complained of non-

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specific diarrhoea, for which no cause was found. His cardiac status as assessed by clinical examination was unchanged. In particular, he was normotensive, and we could find no change from the previous electrocardiogram.

At the age of 42 he entered a standard 26 mile marathon race on 7 February 1976. During this race he complained that he felt ill and that he wished to stop. He continued running, however, and shortly after the 20 mile mark, was found lying supine at the side of the road. There was no evidence of spontaneous respiration and all attempts at resuscitation failed.

A medico-legal necropsy was performed 48 hours later. No naked eye cause to explain the sudden death was found. In particular, there was no intracranial, intrathoracic or intra-abdominal bleeding nor was pulmonary embolism found. The lungs showed acute oedema.

The heart (Fig. 1) was submitted to us for examination 7 hours after necropsy, having been kept on ice for that time. It weighed 460 g and the left ventricular free wall was 2·4 cm thick. The hypertrophy was concentric in nature. The interventricular septum measured 1·3 cm in thickness, giving a septum to free wall ratio of 0·54. The aorta was slightly dextroposed and a sigmoid septum was present. A 2 mm diameter ventricular septal defect passed from below the right coronary cusp of the aortic valve to open on the inferior edge of the crista supraventricularis. The severe degree of myocardial hypertrophy seen in this heart was clearly disproportionate to the small ventricular septal defect.

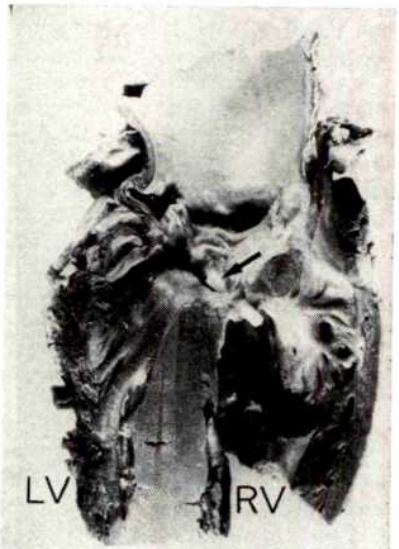

Fig. 1 *Posterior view of aorta, aortic valve, and transected interventricular septum. A probe (arrow) passes through the ventricular septal defect from left ventricle (LV) to right ventricle (RV). The free wall of the left ventricle and the apex have been removed from the specimen.*

The heart valves appeared normal. No endocardial lesions were present, apart from a small jet lesion adjacent to the right ventricular ostium of the septal defect. The coronary arteries showed no significant atherosclerosis and the great arteries were normally related.

Numerous sections from all portions of the heart were examined and most showed hypertrophied myofibres only. However, in several sections of left ventricle (septum and free wall) there were foci of myofibril disarray (Fig. 2) of the type seen in hypertrophic cardiomyopathy. The histological hypertrophic obstructive cardiomyopathy index (Van Noorden *et al.*, 1971) applied to such areas came to over 50 per cent.

Multiple drill biopsies taken from numerous sites in the left ventricle were submitted for biochemical analysis of potassium to sodium (K^+/Na^+) ratios (Table). The myocardial K^+/Na^+ ratio starts to fall within minutes of the onset of severe ischaemia (Nayler *et al.*, 1971) long before histological features of infarction (Rose *et al.*, 1976) are apparent. A potassium to sodium ratio below 1·1 is considered by McVie (1970) to be diagnostic of myocardial infarction. The finding that 8 of the 14 biopsies taken in this patient were below this value seems to indicate myocardial ischaemia, but we cannot exclude the possibility that hypertrophic cardiomyopathy *per se* causes or predisposes to myocardial ionic imbalance.

Discussion

Ventricular hypertrophy is an accepted consequence of prolonged athletic training (Gott *et al.*, 1968). The introduction of echocardiography has, however, disclosed that structural adaptation in the heart differs in response to different exercise types.

Athletes involved in prolonged dynamic exercise such as swimming and running increase their end-diastolic left ventricular internal dimensions without an increase in ventricular wall thickness (Morganroth *et al.*, 1975). On the other hand, shotputters and wrestlers, involved in static exercise, develop an increased left ventricular wall thickness without a change in end-diastolic left ventricular volume. These findings have been related to the stimuli acting during the different exercises; dynamic exercise produces, like valvular incompetence, a

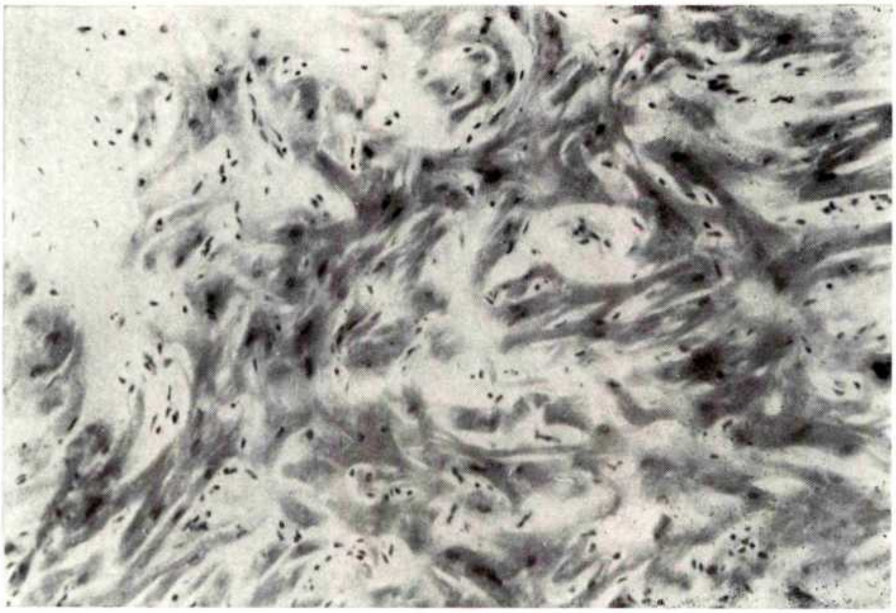

Fig. 2 *Area of myofibril disarray and whorling in free wall of left ventricle. Increased amount of interstitial tissue is present. (Haematoxylin and eosin. × 150.)*

Table *Relation between biopsy sites and myocardial K^+/Na^+ ratios in patient with hypertrophic cardiomyopathy*

*Biopsy number**	*K (mmol/l) fresh weight*	*Na (mmol/l) fresh weight*	K^+/Na^+†
Site A: Between anterior descending and circumflex coronary artery			
1	60·2	126·2	0·47
2	68·5	52·8	1·29
3	67·4	56·7	1·18
4	68·4	46·7	1·46
5	69·3	49·3	1·40
Site B: Posterior to circumflex coronary artery			
6	60·9	64·8	0·93
7	67·9	58·9	1·15
8	59·5	62·5	0·95
9	66·5	58·4	1·13
10	64·8	62·1	1·04
11	77·5	75·0	1·03
Site C: Septum			
12	71·0	90·6	0·78
13	72·6	70·3	1·03
14	80·5	78·7	1·02

*Biopsies were taken 55 hours after death by the drill biopsy method of Pool *et al.* (1968) and analysed for myocardial K^+/Na^+ ratios by the method of Jennings *et al.* (1957).

In each group, biopsies were numbered starting at the base of the heart and working towards the apex.

†A K^+/Na^+ ratio above 1·1 is normal, whereas values below 1·1 indicate myocardial infarction (McVie, 1970). For a discussion on the significance of decreased myocardial K^+/Na^+ ratio see Rose *et al.* (1976) and Raiskina *et al.* (1977).

volume overloaded heart, while during static exercise the heart must work against an increased pressure load.

In contrast to the findings in normal runners, the athlete here reported had a distinct increase in the left ventricular free wall thickness and the necropsy appearance of a small intraventricular volume; these findings would be more compatible with a pressure-overloaded heart. As the patient was normotensive (blood pressure 110/60 mmHg) and had not trained with static exercise, these would constitute unlikely explanations for the ventricular hypertrophy. In addition, the septal defect (2 mm in diameter) was clinically and pathologically too small to have caused such hypertrophy by itself.

The finding of uniform cardiac hypertrophy with the histological pattern of myofibril arrangement as seen in hypertrophic obstructive cardiomyopathy, but unassociated with disproportionate septal hypertrophy, is considered by Davies (1975) to be a not uncommon variant. We have encountered 4 such patients at necropsy in whom this abnormal myofibril arrangement was associated with sudden unexpected death and we consider this to be a further example. Knieriem *et al.* (1975) report a similar case which they label hypertrophic nonobstructive cardiomyopathy. As the presence or absence of left ventricular outflow obstruction, which may in any case have been present only intermittently if at all during life, cannot be determined by necropsy, the term hypertrophic cardiomyopathy more accurately describes our own findings.

The concept of hypertrophic cardiomyopathy as a genetic myocardial disease has been questioned by Bulkley *et al.* (1977) and Come *et al.* (1977) who report patients with either histological or clinical evidence of hypertrophic obstructive cardiomyopathy but without asymmetrical septal hypertrophy. They suggest that haemodynamic factors may be important in the genesis of this group of conditions. We do not know whether haemodynamic factors associated with marathon running could (in the presence of mild congenital cardiac defects) have contributed to the development of the cardiomyopathy in this patient, or whether the inotropic stimulus of exercise may have caused or increased left ventricular outflow obstruction, particularly during the final race.

Suggestive evidence against a familial explanation for this athlete's cardiomyopathy was the failure to find any clinical, radiological, or echocardiographic evidence for this condition in other members of his family (1 brother, 1 sister, 2 sons, 3 nephews).

The important practical point arising from this report is that the athlete chose to ignore his symptoms and to conceal these from his doctors, lest he be forced to stop running. This attitude is identical to that shown by a group of marathon runners who developed myocardial infarction (Noakes *et al.*, 1977), all of whom, exactly like other sportsmen (Opie, 1975), had chosen to ignore warning symptoms. We stress that marathon runners should be aware that they are not immune to cardiac death and that symptoms suggestive of myocardial ischaemia must be investigated.

We are indebted to Dr E. G. J. Olsen of the National Heart Hospital, London, and Dr J. E. Edwards of St Paul, Minnesota, for reviewing the myocardial histology.

We thank Dr T. G. Armstrong of the Cardiac Unit, University of Natal, Durban; Professor J. B. Barlow and Dr A. Davidoff of the Cardiac Clinic, University of Witwatersrand, Johannesburg, and Dr Maurice Nellen, London, who investigated family members of the deceased.

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Requests for reprints to Dr T. D. Noakes, MRC Ischaemic Heart Research Unit, Department of Medicine, University of Cape Town Medical School, Observatory 7925, South Africa.

British Heart Journal, 1979, **41**, 628-629

Polymyositis and complete heart block

JOHN M. REID AND RONALD MURDOCH

From the Department of Cardio-Thoracic Surgery, Mearnskirk Hospital, Glasgow, and the Department of Medicine, Heathfield Hospital, Ayr

SUMMARY The development of complete heart block is described in a patient with polymyositis. The implantation of a permanent pacemaker has controlled the heart block, but the progression of the underlying disease despite treatment with relatively high dosage of corticosteroids makes the outlook uncertain.

Although involvement of the myocardium in polymyositis has been recorded (Garcin *et al.*, 1955), cardiac involvement is a relatively uncommon accompaniment in this condition (Hill and Barrows, 1968). The association of complete heart block and polymyositis is exceptional, and we wish to record such an event occurring in a patient four years after the onset of muscle pain and weakness.

Case report

A man aged 37 years first developed pain and stiffness in both thighs in 1973. This was followed by effusion in the right knee joint. Examination on admission to hospital revealed pronounced muscle wasting in both thighs. The latex test for rheumatoid arthritis, ASO titre, WR and VDRL, ESR, serum calcium and phosphate, alkaline phosphatase, protein electrophoresis, and thyroid scan were all negative, as was radiological examination of the spine and both knees. Subsequently the creatinine kinase (CK) was found to be increased at 644 mIU/l (normal < 50 mIU/l), and muscle biopsy showed foci of muscle fibre necrosis and regeneration, associated with patchy interstitial chronic inflammatory infiltrate. The appearances were consistent with polymyositis, and treatment was instituted with prednisolone, starting with 100 mg daily and reducing to 20 mg daily as maintenance. His condition over the next four years alternated between remissions and relapses necessitating temporary increases in the dosage of corticosteroids. The CK remained persistently high in the range 644 to 5400 mIU/l and the aldolase was greater than 60 mIU/l (normal < 50 mIU/l). At no time was there any skin involvement. Serial electrocardiograms remained normal from 1973 until mid 1976, when the first evidence of conduction disturbance was noted on the electrocardiogram. The PR interval was 0·18 s, there was left axis deviation with a QRS axis of −60°, there was poor progression of the R wave in right praecordial leads, absence of Q waves in left praecordial leads, QRS of 0·16 s, and the resting heart rate was 55 per minute. He remained symptom-free until mid 1977, when he began to experience dizziness accompanied on several occasions by temporary loss of consciousness. On admission to hospital the electrocardiogram now showed complete heart block, with a ventricular rate of 32 per minute, right axis deviation, and the QRS was 0·20 s. Facilities were not available at the time to perform intracardiac electrocardiography to try and define more precisely the exact site of the block. There were no murmurs audible on auscultation, and chest *x*-ray film showed no cardiac enlargement. A permanent lithium iodide (Medtronic 5972) pacemaker with endocardial electrode was inserted without incident. When reviewed 6 months later, he was pacing satisfactorily. However, because of generalised muscle weakness and high CK levels, the dosage of corticosteroids had to be increased once more.

Discussion

Various complications may ensue during the course of polymyositis, including ophthalmoplegia, interstitial pulmonary fibrosis, renal failure, and carcinoma of colon (Vukotic and Bozovic, 1975). Cardiac involvement, however, is uncommon (Babka and Pepine, 1973). These authors reported the development of a hyperkinetic cardiovascular state, with congestive cardiac failure refractory to treatment with digoxin and diuretics, in a patient with polymyositis. At necropsy the heart was microscopically normal and excess catecholamines released by degenerating muscle were postulated as the cause of the hyperkinetic state. Lynch (1971) reported the development of complete heart block in a patient three years after the onset of the first symptoms of polymyositis. Treatment with corticosteroids and the implantation of a cardiac pacemaker produced only temporary benefit, and the patient died suddenly shortly afterwards. Detailed necropsy studies revealed replacement fibrosis of cardiac muscle fibres in both ventricles, no abnormality in the atrioventricular node, but some fibrosis in both the bundle of His and its two major branches.

In our patient heart block was first noted four years from the onset of muscle weakness, though the electrocardiogram one year previously had indicated the onset of conduction disturbance. There was first degree block, possible left anterior fascicular block, and early left bundle-branch block. There appeared to be no other cardiac involvement and there was no cardiomegaly, so the outlook should be good now that a pacemaker has been implanted. Though high-dose corticosteroids have suppressed the symptoms of polymyositis to date, the persistence of raised levels of both CK and aldolase indicate continuing progression of the underlying disease process, and the long-term prognosis remains problematic.

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Correspondence

British Heart Journal, 1979, **41**, 630

Near fatal puerperal thrombosis on Björk-Shiley mitral valve prosthesis

Sir,

We agree with McLeod *et al.* (*British Heart Journal*, 1978, **40**, 934-937) that biological valves should remain the prosthesis of choice in young women. We are intrigued by their decision to change to heparin at 17 weeks; the change should be made earlier to ensure against fetal malformation. However, the circumstances in this case presenting at 10 weeks' gestation may have placed the authors in a difficult clinical situation. There is no doubt that a small number of patients with prosthetic heart valves develop occlusive thrombosis of the valve in spite of adequate anticoagulation; the risk is even greater during pregnancy. While agreeing with the conventional concept of heparin in early pregnancy, this patient could have been switched to warfarin in the second trimester and back to heparin before labour. In addition, especially with a mitral disc valve, an antiplatelet drug like dipyridamole in a dose of 300 to 400 mg/day may be a necessary safeguard. This drug does not increase the risk of bleeding at this dose and can only complement the action of subcutaneous heparin. This has been our practical approach to the problem. Though subcutaneous heparin may be an acceptable form of prophylaxis in venous thrombosis, it may not afford adequate protection in the dose and route used in the prevention of thrombosis in the arterial circulation.

S. M. Rajah,
Suba Rao,
R. Ahmad,
and D. A. Watson,
Leeds Regional Thoracic Surgical Centre,
Killingbeck Hospital,
Leeds LS14 6UQ.

This letter was shown to the authors who reply as follows:

Sir,

We are interested in the practical approach by the Leeds group to the problem of managing heart valve prostheses in pregnancy. We agree that the addition of dipyridamole seems a sensible plan since there is some objective evidence of its efficacy when added to conventional warfarin therapy. However, there is only anecdotal evidence of its efficacy as a sole protective agent in this situation.

The patient discussed in our paper was, we agree, changed to heparin at too late a date in pregnancy to protect fully against fetal malformation. Unfortunately this matter was out of our hands. Obviously the ideal would be to use heparin prospectively in patients who are planning a pregnancy, and we await the results of further studies of antiplatelet drugs with interest.

A. A. McLeod,
K. P. Jennings,
and E. R. Townsend,
King's College Hospital,
Denmark Hill,
London SE5 9RS.

British Heart Journal, 1979, **41**, 631

Echocardiographic identification of aorta and main pulmonary artery in complete transposition

Sir,

A. B. Houston *et al.* (*British Heart Journal*, **40,** 377-382) describe the echocardiographic identification of aorta and main pulmonary artery in complete transposition with beautiful pictures.

It is easy to identify the aorta in transposition if you can recognise the brachiocephalic trunk arising from the anterior vessel. This is particularly so in the more complex anomalies such as transposition with pulmonary atresia. Strangely enough, Houston does not mention this sign though his Fig. 4 (page 379) is a beautiful example.

O. Daniëls,
Dept. of Paediatric Cardiology,
Universiteitsklinik voor Kindergeneeskunde,
Nijmegen,
Holland.

This letter was shown to Dr Houston and his co-authors who reply as follows:

Sir,

We agree with Dr Daniëls, but since we have not always been able to visualise the brachiocephalic trunk (innominate artery) we have been unwilling to put this forward as a feature on which we may depend when identifying the aorta.

A. B. Houston,
N. L. Gregory,
and E. N. Coleman,
Royal Hospital for Sick Children,
Yorkhill,
Glasgow G3 8SJ.

Erratum

Volume 40 (1978) pages 1306-1309: the authors have asked us to point out an error in their paper on 'Incidence of thyroid disease in cases of hypertrophic cardiomyopathy'. On page 1308, line 13 of the Discussion, the word 'largely' was printed in error for 'large'.

Notices

British Heart Journal, 1979, **41**, 632

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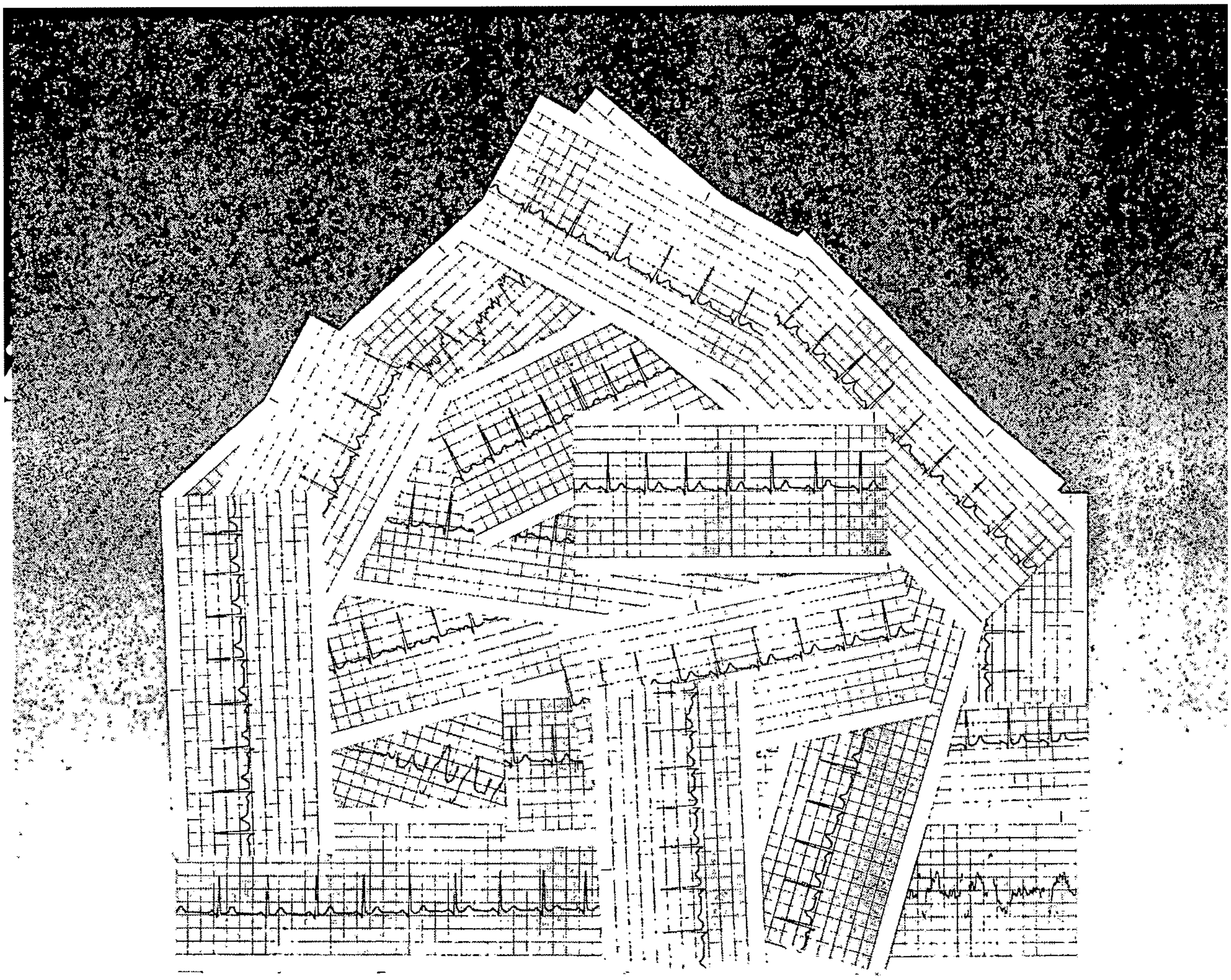

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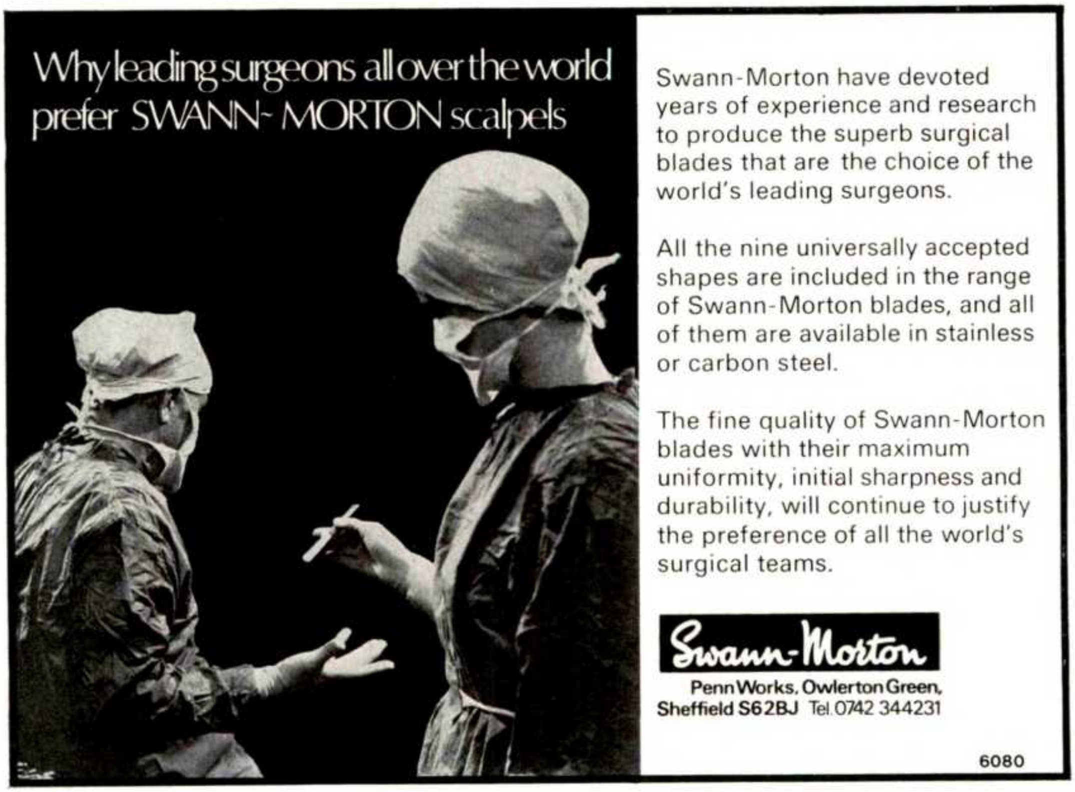

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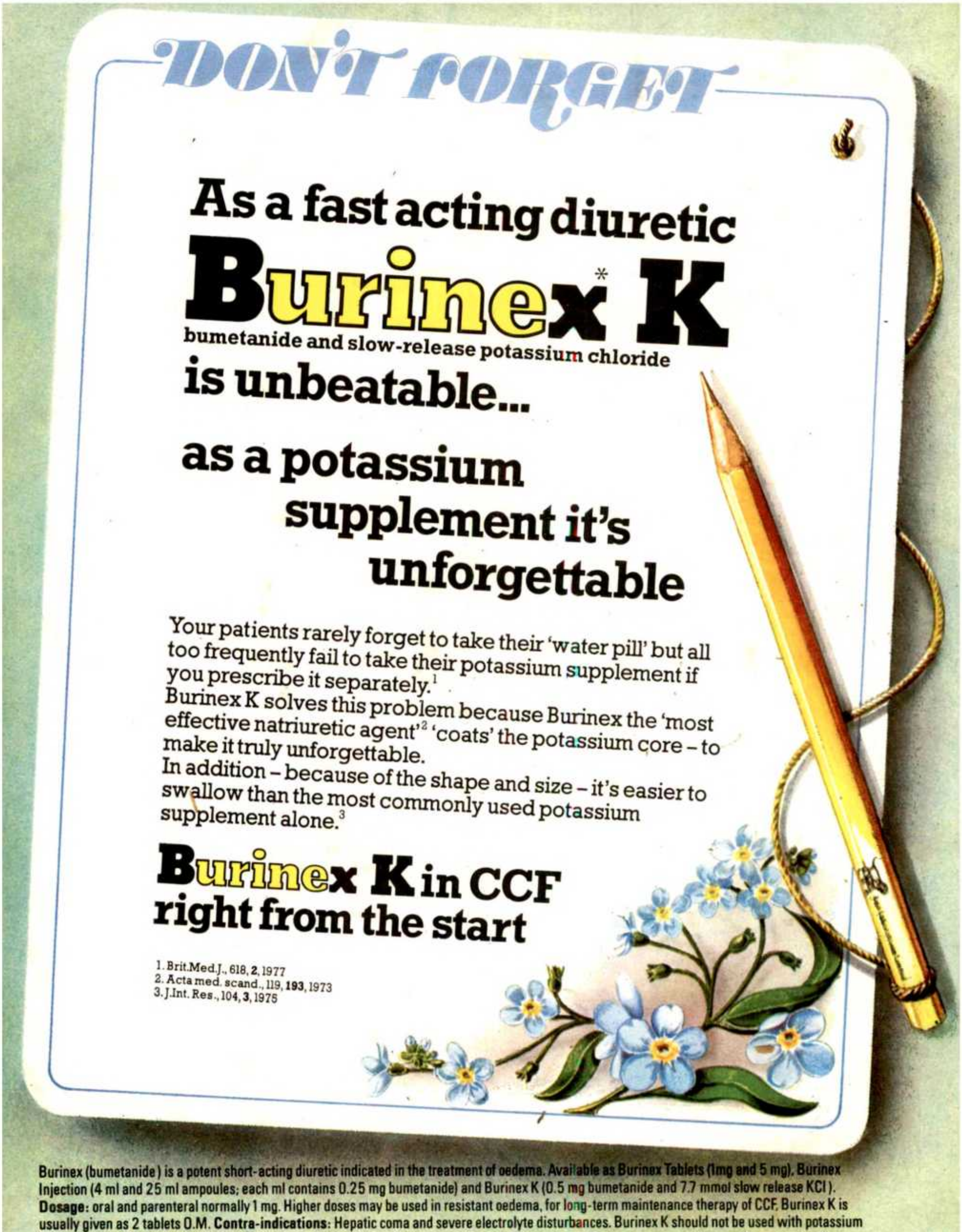

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1. Brit.Med.J., 618, **2**, 1977
2. Acta med. scand., 119, **193**, 1973
3. J.Int. Res., 104, **3**, 1975

Burinex (bumetanide) is a potent short-acting diuretic indicated in the treatment of oedema. Available as Burinex Tablets (1mg and 5 mg), Burinex Injection (4 ml and 25 ml ampoules; each ml contains 0.25 mg bumetanide) and Burinex K (0.5 mg bumetanide and 7.7 mmol slow release KCl). **Dosage:** oral and parenteral normally 1 mg. Higher doses may be used in resistant oedema, for long-term maintenance therapy of CCF, Burinex K is usually given as 2 tablets O.M. **Contra-indications:** Hepatic coma and severe electrolyte disturbances. Burinex K should not be used with potassium sparing agents. **Adverse reactions:** Occasional skin rashes and minor gastric upset. **Precautions:** Burinex may potentiate antihypertensive therapy and rarely, may affect carbohydrate metabolism. Periodic electrolyte checks are advisable on long-term therapy. Burinex K should be stopped immediately if signs or symptoms of bowel ulceration appear. **Product Licence No:** 0043/0027B

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June 1979 Vol 41 No 6

British Heart Journal

A monthly journal of cardiology
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Prognosis of patients paced for chronic atrioventricular block *W. Ginks, A. Leatham, and H. Siddons* 633

Complete right bundle-branch block. Echophonocardiographic study of first heart sound and right ventricular contraction times *N. Brooks, G. Leech, and A. Leatham* 637

Patients treated in a coronary care unit without acute myocardial infarction. Identification of high risk subgroup for subsequent myocardial infarction and/or cardiovascular death *R. Nordlander and O. Nyquist* 647

Reduction of early ventricular arrhythmia by acebutolol in patients with acute myocardial infarction *Gail G. Ahumada, R. P. Karlsberg, A. S. Jaffe, H. D. Ambos, B. E. Sobel, and R. Roberts* 654

Recognition and quantification of myocardial injury by means of plasma enzyme and isoenzyme activities after cardiac surgery *A. van der Laarse, H. A. Davids, L. Hollaar, E. J. M. van der Valk, S. A. G. J. Witteveen, and W. Th. Hermens* 660

Estimation of myocardial infarct size in man using 99^{m} Tc polyphosphate *G. J. Davies, B. Fakhrai, A. Morgan, and J. R. Muir* 668

Uhl's anomaly *R. J. Vecht, D. J. S. Carmichael, R. Gopal, and G. Philip* 676

Maximal supine exercise haemodynamics after open heart surgery for Fallot's tetralogy *Gordon R. Cumming* 683

Antibodies to Coxsackie B viruses in congestive cardiomyopathy *G. Cambridge, C. G. C. MacArthur, A. P. Waterson, J. F. Goodwin, and C. M. Oakley* 692

Heart size and function in acromegaly *H. M. Mather, M. J. Boyd, and J. S. Jenkins* 697

Long-term follow-up in primary pulmonary hypertension *L. D. Suarez, E. E. Sciandro, J. J. Llera, and A. M. Perosio* 702

Clinical electrophysiological effects of propranolol on normal sinus node function *M. Vasquez, R. Chuquimia, N. Shantha, M. Khan, and O. S. Narula* 709

Comparability and reproducibility of apex cardiogram recorded with six different transducer systems *J. L. H. Willems, B. Denef, H. Kesteloot, and H. De Geest* 716

Case reports

- A severe complication of pulmonary vein angiography *Bruce S. Alpert and J. A. Gordon Culham* 727
- Mitral valve replacement for mitral stenosis caused by Libman-Sacks endocarditis *K. C. Vaughton, D. R. Walker, and M. F. Sturridge* 730
- Alternating atrial and ventricular tachycardia *R. M. Jordan, J. H. McAnulty, and L. Ritzmann* 734

Obituary: Arthur Morgan Jones 738

Correspondence 740

Index 741

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British Heart Journal

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SI units The units in which the authors' work was measured should be cited first followed by either the SI units or the traditional units. This does not apply to Tables, but here a conversion factor should be added as a footnote.

Case reports These are intended only briefly to convey the essential facts of a case, and discussion and bibliography should be kept to a minimum. These papers should have no more than 3 authors, should not exceed 1500 words, and should contain no more than 2 Figures.

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Illustrations These should be identified on the back with Figure number of Arabic numerals, title of paper, and name of author. The legends should be typed on a separate sheet of paper. The Figures should be on glossy paper and unmounted unless several are grouped together in a composite Figure, as in montage. Any lettering to be inserted should be indicated lightly in pencil on a transparent overlay. *Diagrams, charts* and *line drawings* should be drawn in India ink. *Electrocardiograms, etc.* Only black and white electrocardiograms make satisfactory blocks, and if the originals are sent they should be protected by a covering of transparent paper. If several electrocardiograms are grouped in a single Figure, only a few complexes should be shown, and the width should not exceed 5½ inches unless a reduction in scale is feasible. Authors submitting *x-ray pictures* with their manuscripts are asked to ensure that they conform to the standards set out in the Editorial in the Journal, vol. 35, page 1101.

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oxprenolol hydrochloride BP plus cyclopenthiazide BP

Once daily in hypertension

- **Prescribing Notes**

Presentation Trasidrex tablets each contain 160mg oxprenolol hydrochloride BP in a sustained-release formulation and 0.25mg cyclopenthiazide BP in the sugar coat.

Indications In the treatment of mild and moderate hypertension. The combination product may be suitable for use when satisfactory control of arterial blood pressure cannot be obtained with either a diuretic or a beta-blocking drug used alone.

Dosage *Adults:* One or two tablets once daily. Trasidrex can be combined with other antihypertensive drugs having a different pharmacological effect. In particular, a free combination with a vasodilator (e.g. Apresoline®) will often be beneficial.

Side effects Though mild gastro-intestinal upsets and dizziness may occur, especially at the start of treatment, they are rarely sufficiently severe to justify withdrawal of therapy. Drowsiness and insomnia occur infrequently. As with all beta-blockers bronchospasm, cold extremities, excess bradycardia and heart failure could be precipitated in susceptible patients.

Beta-blockers are occasionally associated with skin rashes and/or dry eyes. If any such reaction is suspected, treatment should be withdrawn gradually.

In common with other thiazides there have been reports of thrombocytopenia but these are rare. Thiazides can produce allergic skin reactions, mild anorexia and nausea and cause latent gout or latent diabetes to become manifest.

Precautions Cardiac failure must be controlled by digitalis before and during Trasidrex therapy. Caution should be observed when treating asthmatics, chronic bronchitics or other individuals where bronchospasm may be precipitated. Trasidrex should be given cautiously to patients with metabolic acidosis, or renal impairment and during anaesthesia. Beta-blockers may mask the symptoms of hypoglycaemia and affect carbohydrate metabolism. Thiazides may also decrease glucose tolerance. Therefore, in patients with diabetes it may be necessary to adjust the dosage of anti-diabetic medication. Sudden withdrawal of any beta-blocking drug may induce or worsen angina pectoris.

Pregnancy Beta-blockers may cause bradycardia in the fetus, which can also persist after birth. During late phases of pregnancy and in the course of labour, beta-blockers should only be employed after the needs of the mother have been weighed against the possible risks to the fetus.

Contra-indications Patients with atrio-ventricular block, marked bradycardia, uncontrolled heart failure, cardiogenic shock, renal insufficiency and during concomitant lithium treatment.

Packs Cartons of 28 tablets consisting of two reminder calendar foils of 14 tablets — Basic NHS price 28: £7.12

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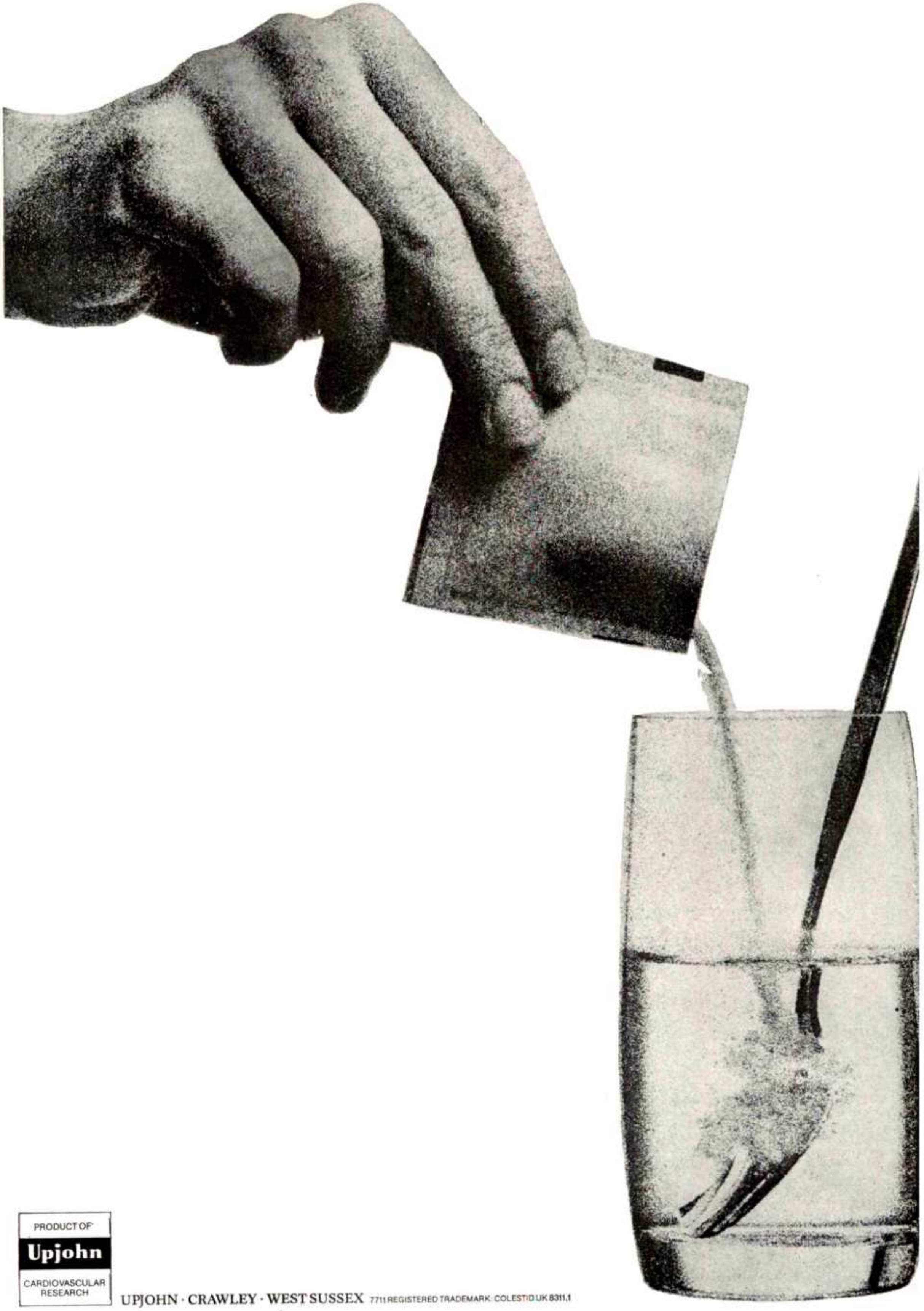

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Colestid

colestipol

a non-systemic agent from Upjohn which lowers serum cholesterol

Many authorities agree that elevated serum cholesterol is an important factor in the development of atherosclerosis. And, while it is not yet possible to assume that lowering cholesterol will reduce morbidity from coronary heart disease, most physicians accept the importance of maintaining serum cholesterol levels as close to normal as possible.

Colestid (colestipol), a new non-systemic agent developed by Upjohn research, effectively lowers serum cholesterol by an average 12–15% in Type II hyperlipidaemic patients – those with elevated cholesterol and normal or slightly elevated triglycerides.[1,2,3] A lowering of serum cholesterol by 19% has been demonstrated with 10 grams of Colestid given twice a day.

Colestid achieves a reduction in serum cholesterol by interfering with the normal enterohepatic circulation of bile acids. Bile acids are synthesised in the liver from cholesterol and are secreted in bile into the intestine. Colestid works in the intestinal lumen, binding these bile acids and increasing the rate of their excretion. Less bile acid is available for reabsorption from the intestine, and the liver must convert additional cholesterol to bile acid. The result is a reduction in plasma cholesterol levels.

Unlike other resin preparations, Colestid is well accepted by most patients. The odourless, tasteless granules may be mixed with a variety of liquids and foods, including fruit juices, milk, soups, pulpy fruits with a high water content, and carbonated beverages.

Colestid has produced no known interference with the action of coumarin anticoagulants, making it suitable for patients already under treatment for a heart condition. However, since Colestid may interfere with the absorption of certain drugs (e.g., chlorothiazide, tetracycline and penicillin G), the clinical response to concomitant medications should be closely monitored and appropriate adjustments made.

Most patients tolerate Colestid therapy very well. The most common side effect is mild constipation.

References: 1. Med. J. Aust. (1973). *1*:1223.
2. JAMA (1972). 222:676.
3. New Zealand J. Med. (1972). 76:12.

Prescribing Information

Presentations: Tasteless and odourless granules of colestipol hydrochloride. *Uses:* Adjunctive therapy to diet for treatment of hypercholesterolaemia, particularly Frederickson Type II. *Dosage and Administration:* Always mix with water or other fluids before ingesting. Oral total daily dosage for adult 15–30 grams. Take in divided doses 2–4 times daily. *Contraindications:* Hypersensitivity to colestipol. *Precautions, Warnings:* Not to be taken in dry form. Colestid may interfere with absorption of some drugs (e.g. penicillin G, tetracycline, chlorothiazide). Safety for use in pregnant women or children not established. *Package Quantities:* 30 x 5 g sachets; 250 g bottle. Each sachet or scoopful contains 5 g colestipol hydrochloride. *Further Information:* Colestid is not absorbed. It binds bile acids causing further cholesterol conversion to bile acids thus lowering serum cholesterol levels. *Basic NHS Costs:* 30 x 5 g sachets £8.90. 250 g bottle £13.76. Product Licence Nos. PL 0032/0055. PL 0032/0057. *Full Product information is available on request.*

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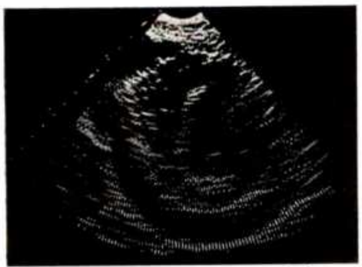
Left ventricular hypertrophy, pericardial effusion.

Normal

Pericardial effusion.

Inferior Vena Cava entering right atrium.

Normal

Tricuspid valve vegetation.

Small pericardial effusion, long axis view.

Pericardial effusion, short axis view.

Tricuspid valve vegetation.

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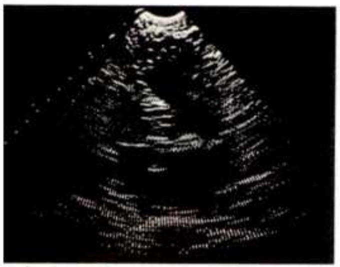

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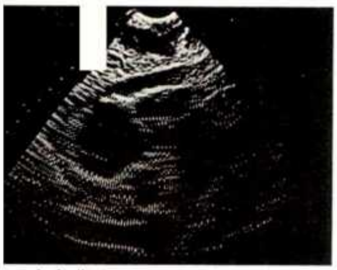

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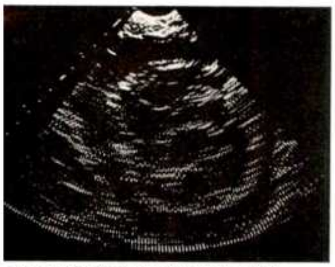

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Fighting disease with Electronics

6 U.S. expert committees have now reported on diet and heart disease.

6 recommend partial substitution of saturated fats by polyunsaturated fats.

1	Inter-Society Commission for Heart Disease Resources 1970. "Primary prevention of atherosclerotic diseases."	✓	4	American Medical Association Council on Foods and Nutrition 1972. "Diet and Coronary Heart Disease."	✓
2	American Health Foundation 1972. "Diet and Coronary Heart Disease."	✓	5	Select Committee on Nutrition and Human Needs 1977. "Dietary goals for the United States."	✓
3	White House Conference 1973. "Nutrition policies in the Seventies."	✓	6	American Heart Association Committee on Nutrition 1978. "Diet and Coronary Heart Disease."	✓

The most recent of these committees* recommends that…

"The proportion of saturated fatty acids in the diet be brought into proper balance.

"To this end the levels of saturated fatty acids should be decreased to less than 10% of the total calories… Polyunsaturated fatty acids should supply up to 10% of the total calories, which can be accomplished easily."

Flora margarine is made with pure sunflower oil. It is higher in polyunsaturates than any other nationally available spread and the lowest in saturated fat.

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*American Heart Association 1978. "Diet and coronary heart disease." General dietary recommendations - Section 2.

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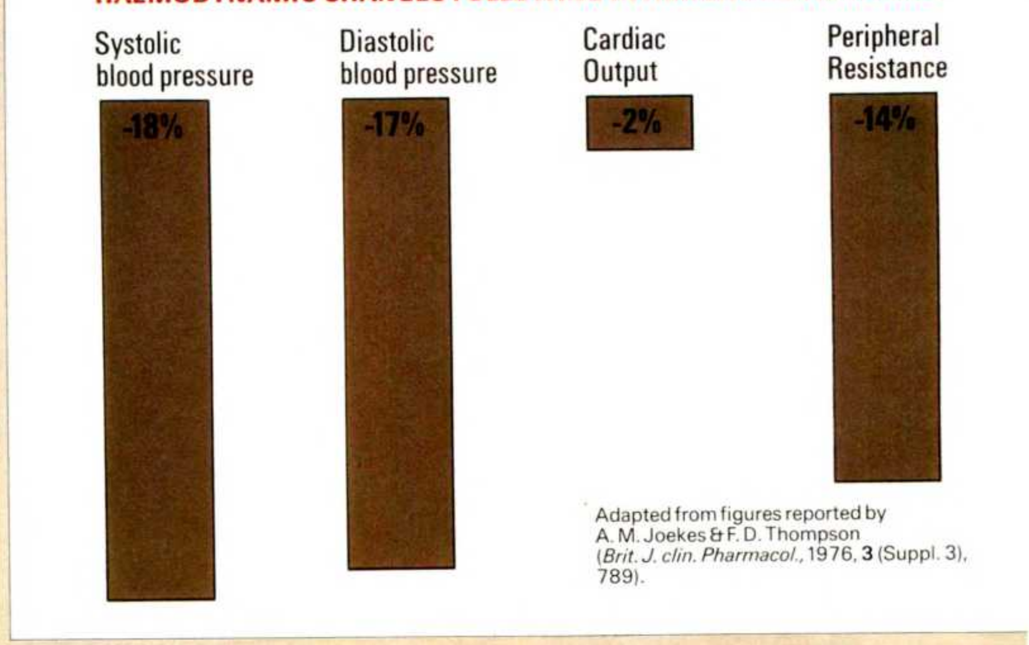
Trandate

(labetalol hydrochloride)

has the right haemodynamic profile


HAEMODYNAMIC CHANGES FOLLOWING INTRAVENOUS TRANDATE

Adapted from figures reported by A. M. Joekes & F. D. Thompson (*Brit. J. clin. Pharmacol.*, 1976, **3** (Suppl. 3), 789).

The above figure shows the mean haemodynamic changes in 14 hypertensive patients given intravenous Trandate 0.5-1.0mg/kg

In essential hypertension the usual haemodynamic changes are increased blood pressure and peripheral resistance while cardiac output remains normal.

The authors of the above trial reported:
"Although there are striking changes in the blood pressure, this can be largely attributed to a fall in peripheral resistance with little change in pulse rate, stroke volume or cardiac output."

INTRAVENOUS TRANDATE
reduces blood pressure and peripheral resistance
without significantly affecting cardiac output

come down fast...

INJECTION

Trandate Injection provides rapidly effective control of hypertensive emergencies

AS A BOLUS INJECTION...

"Labetalol given intravenously is highly effective for the acute reduction of blood pressure. In this series no serious side effects were encountered and the drug seems particularly suitable for use in hypertensive emergencies." (Rosei, E. A. et al, *Clin. Sci. mol. Med.*, 1976, **51**, 497s)

OR AS A CONTINUOUS INFUSION...

"Labetalol, given slowly by graded intravenous infusion, with continuous monitoring of arterial pressure, is our current treatment of choice in hypertensive emergencies." (Brown, J. J. et al, *Lancet*, 1977, **i**, 1147)

Subsequent treatment can be continued with the same drug given orally

"A practical advantage associated with labetalol is that oral treatment can be instituted immediately after using the intravenous form."

(Rønne-Rasmussen, J. O. et al, *Brit. J. clin. Pharmacol.*, 1976, **3** (Suppl. 3), 805)

"There are many advantages to using a compound that can be given intravenously to control blood pressure in patients with small vessel disease or impaired renal function, which is then available for long-term oral therapy."

(Joekes, A. M. & Thompson, F. D., *Brit. J. clin. Pharmacol.*, 1976, **3** (Suppl. 3), 789–793)

Trandate Tablets provide effective therapy in all grades of hypertension – including the difficult cases

"In this study (oral) labetalol reduced the blood pressure significantly in a group of patients with severe, drug-resistant hypertension."

(Morgan, T. et al, *Med. J. Australia*, 1978, **i**, 393)

"Complete control of the blood pressure could hardly be expected in this group of patients and it was rewarding to obtain a very useful reduction in both the systolic and diastolic pressures in such a high percentage with a simple treatment regimen (oral Trandate)."

(Altman, M., *J. Pharmacotherapy*, 1978, **1**, 208)

Trandate

THE FIRST ALPHA-BETA-BLOCKER

RIGHT IN PRINCIPLE - WORKING IN PRACTICE

PRODUCT INFORMATION

PRESENTATION

Trandate Tablets 100mg, 200mg and 400mg each contain labetalol hydrochloride, 100mg, 200mg and 400mg respectively. In packs of 50 and 250. PL 0045/0106, PL 0045/0107 and PL 0045/0109.
Trandate Injection: 20ml ampoules each containing 100mg (5mg/ml) labetalol hydrochloride. In boxes of 5 ampoules. PL 0045/0104.

INDICATIONS

Trandate Tablets are indicated for the oral treatment of all grades of hypertension, mild, moderate and severe.
Trandate Injection is indicated when rapid control of blood pressure is essential.

DOSAGE AND ADMINISTRATION

Trandate Tablets:
Adults: The initial dosage should not usually exceed 100mg 3 times daily. Adjustment of dosage should be gradual. Most cases are controlled with 600mg per day or less, but severe cases may require up to 2,400mg daily. Administration should be after a main meal.

Trandate Injection:
Adults: When rapid reduction of blood pressure is essential a dose of 50mg of Trandate should be given by intravenous injection over at least one minute. This may be repeated, if necessary, at 5-minute intervals but the total daily dose should not exceed 200mg. Alternatively it may be given by intravenous infusion. For this 2 ampoules of Trandate Injection are diluted to 200ml with sodium chloride and dextrose injection BP. This is infused at a rate of 2ml/minute until a satisfactory response is obtained when the infusion should be stopped. For most patients the effective dose is from 50 to 200mg but in phaeochromocytoma up to 300mg may be necessary.

Patients should be in the supine position when Trandate Injection is given and they should not stand or sit up within 3 hours of starting the administration. Once controlled, blood pressure reduction can be maintained with Trandate Tablets at a starting dose of 200mg 3 times daily.
Children: Not applicable.
For information on the use of Trandate with other drugs or for transfer to Trandate from other antihypertensive agents, see respective Data Sheets.

CONTRA-INDICATIONS, WARNINGS, ETC.

Trandate should not be given to patients with uncontrolled or digitalis-resistant heart failure, or with atrioventricular block. Caution is necessary in asthmatic patients or others prone to bronchospasm. Patients with severe liver damage will probably require lower doses of Trandate than usual. Unnecessary administration of drugs during the first trimester of pregnancy is undesirable.
Trandate Injection may cause excessive postural hypotension if patients are allowed to assume the upright position within 3 hours of administration.
Trandate Tablets may cause symptoms of postural hypotension if initial dosage is too high or increased too rapidly, but they are uncommon, except at very high doses, if used as recommended. Mild and usually transient side effects include: headache, tiredness, dizziness, depressed mood, lethargy, difficulty in micturition, epigastric pain and nausea and vomiting. Tingling in the scalp has occasionally occurred but is usually transient. Rarely, a lichenoid rash has been reported which disappears on drug withdrawal. Other skin rashes, blurring of vision, eye irritation and cramps have been reported but have been difficult to relate directly to Trandate treatment.
Warning: There have been reports of skin rashes and/or dry eyes associated with the use of beta-adrenoceptor blocking drugs. The reported incidence is small and in most cases the symptoms have cleared when the drug was withdrawn. Discontinuance of the drug should be considered if any such reaction is not otherwise explicable. Cessation of therapy with a beta-adrenoceptor blocking drug should be gradual.

Full prescribing information is available on request.

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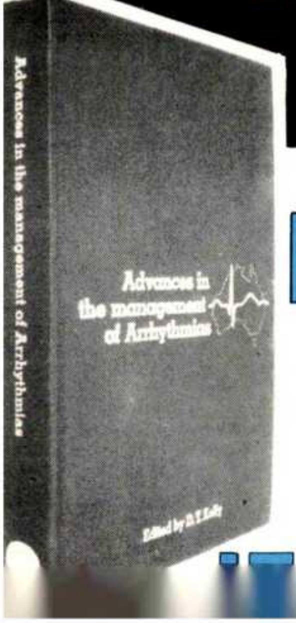
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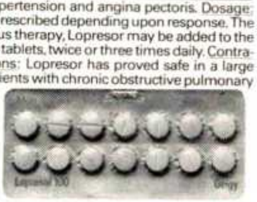

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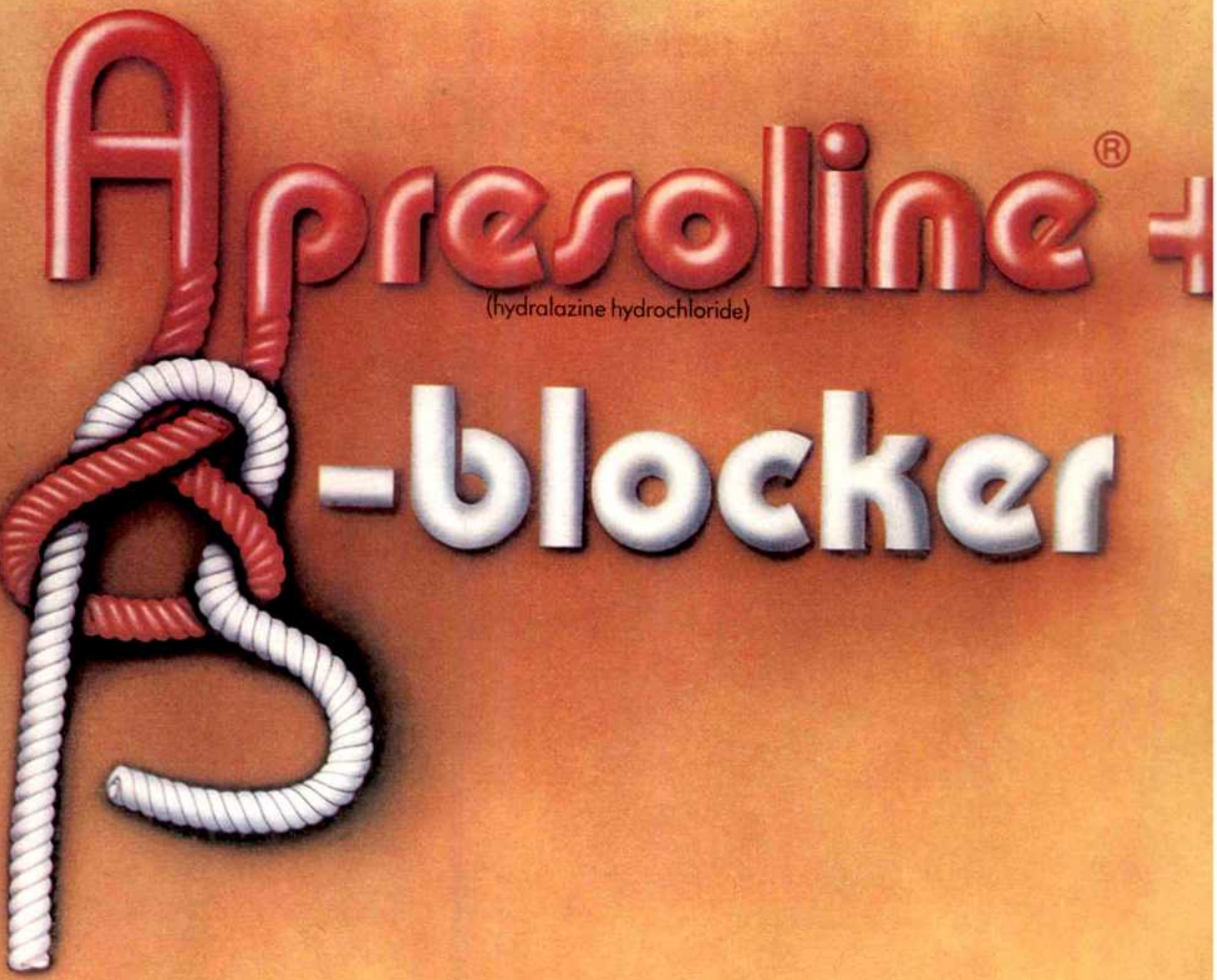

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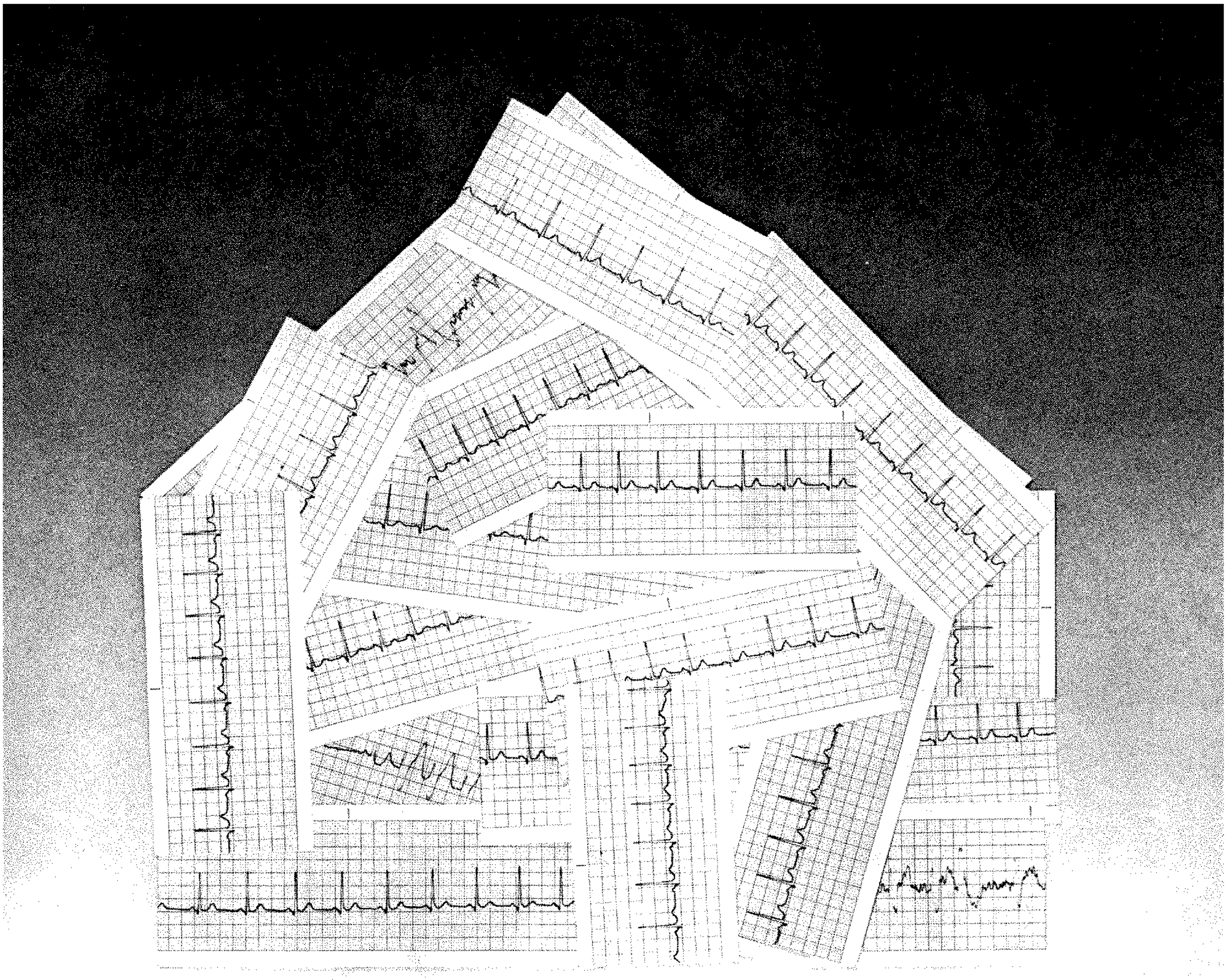

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British Heart Journal, 1979, **41**, 633-636

Prognosis of patients paced for chronic atrioventricular block

WILLIAM GINKS, AUBREY LEATHAM, AND HAROLD SIDDONS

From the Department of Cardiology, St George's Hospital, Hyde Park Corner, London

SUMMARY Between the years 1960 and 1974, 839 patients were paced for chronic complete atrioventricular block.

Analysis of survival compared with the general population showed that 170 deaths were expected according to standard mortality tables and 288 actually occurred, giving a ratio of actual to expected deaths of 1·7:1.

Patients with a definite history of myocardial infarction showed a higher than average mortality when paced. Mortality was not influenced whether heart block was constant or intermittent, whether the ventricular rate was below or above 40/minute, or whether QRS duration was greater or less than 0·1 second.

Analysis of the age groups paced disclosed the most important correlations. Between the ages of 80 and 89 years paced patients could expect to survive as long as others of the same age without heart block. There was, however, a very high mortality ratio of 4·5:1 for 90 patients in the age group 50 to 59 years. The reason for the high mortality ratio was uncertain but it may have been the result of a greater incidence of underlying coronary artery disease.

In 1974, Siddons analysed the survival of patients paced for chronic complete heart block. The comparison was made of 649 paced patients and 113 patients who were unpaced despite chronic atrioventricular block, and the comparison was also made with the survival pattern of the general population. Survival of the paced patients was much better than that of the unpaced group, despite the fact that the unpaced patients were selected as 'good risk cases' in the early 1960's before pacing had become a standard procedure. It was noted that in the first year after the start of pacing the mortality was higher than in subsequent years. It was also noted that survival rate after this first year of pacing was very close to that of the general population matched for age and sex, and for these reasons a more detailed statistical study of the survival of paced patients was undertaken.

Methods

The records of all patients with complete heart block, paced on a long-term basis, were analysed with regard to age and symptoms on initial presentation. In each case attention was drawn to a previous history of syncope, angina, myocardial infarction, and cardiac failure, though in a number of instances some features of the previous history were inadequately documented and analysis of all 839 patients was, therefore, incomplete. Examination of the electrocardiogram was also undertaken in patients where a complete 12 lead electrocardiogram before pacing was available for review. Patients were categorised according to the type of idioventricular rhythm; patients with complete heart block and an idioventricular rhythm with left anterior hemiblock had a mean frontal QRS of greater than −30°; those with an idioventricular rhythm of right bundle-branch block type had a QRS duration of 0·12 s or greater and an rSR′ in lead V1; those with an idioventricular rhythm of left bundle-branch block type had a QRS of 0·12 s or greater and a broad monophasic R wave in lead V6 (New York Heart Association, 1969).

Patients paced for other conditions such as sinuatrial disease without atrioventricular block were excluded. In addition, patients with acute infarction block with early return to sinus rhythm were excluded but we have included a few cases who continued in complete heart block after in-

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Table 1 *Analysis of survival of paced patients compared with the general public matched for age and sex*

		No. of patients	*Years of exposure*	*Actual deaths*	*Expected deaths*	*Mortality ratio*
	Total	839	2872·5	288	169·9	1·7:1
Duration	1st year	839	793·5	114	43·8	2·6:1
	2nd year	640	597·5	56	34·7	1·6:1
	3rd-5th year	504	1039·5	90	64·1	1·4:1
	6th year and up	200	442	28	27·3	1:1
Sex	Male	504	1653	177	107·5	1·7:1
	Female	335	1219·5	111	62·5	1·8:1
Age first paced	50-59	90	404	29	6·5	4·5:1
	60-69	270	1026	90	34·4	2·6:1
	70-79	350	1090·5	119	79·0	1·5:1
	80-89	129	352	50	50·1	1:1
Calendar year of first pacing	1960-1965	105	568·5	73	25·4	2·9:1
	1966-1974	734	2304	215	144·5	1·5:1
Syncope	Syncope	703	2490	243	147·8	1·7:1
	No syncope	132	367	41	21·4	1·9:1
	No record	4				
Angina	Angina	197	730·5	77	38·4	2·0:1
	No angina	599	1996	191	121·4	1·6:1
	No record	43				
Infarction	Infarct	77	245·5	34	11·8	2·9:1
	No infarct	670	2339	214	140·6	1·5:1
	No record	92				
Cardiac failure	Failure	198	533·5	79	39·5	2·0:1
	No failure	545	1996	140	111·8	1·3:1
	No record	96				
Intermittent block	Intermittent	225	889	84	45·6	1·8:1
	Established	614	1983·5	204	124·3	1·6:1

farction. In order to make the series homogeneous and suitable for comparison with the general population we excluded patients under 50 and over 89 years, cases previously paced at other hospitals, patients not living in the United Kingdom, those patients with post-surgical block, and cases paced immediately before operation for carcinoma or severe peripheral vascular disease.

A detailed statistical analysis of the mortality of paced patients was made by the Swiss Re-Insurance Company's Statistical Department. The figures for the general population are taken from the Registrar General's report of 1968 for the South East of England from which the paced patients were drawn.

Results

There were 839 patients paced for chronic atrioventricular block with a presenting symptom of syncope in nearly all cases. The average observation period was 3·4 years and the follow-up to 31 December 1974 was 98 per cent complete. There were 504 men and 335 women.

The analysis of survival compared with the general population is shown in Table 1. In the general population 169·9 deaths were expected according to the standard mortality tables but 288 deaths actually occurred. The ratio of actual over expected deaths of the population of the same age and sex was therefore 1·7:1. This is the average mortality ratio for the whole of the paced series. In the first year of pacing, there was an extra mortality amounting to a ratio of 2·6:1, with 114 deaths when 43·8 were expected in the general population. The outlook for patients who were paced for 5 years matched almost exactly that of the general population. In the first 5 years of our experience (1960 to 1965) during which 105 patients were paced, the outlook was worse than since that date.

As expected those patients with a previous history of myocardial infarction showed a higher than average mortality.

A history of syncope occurred in 703 cases and may have been expected to carry a higher mortality than in the 132 cases without syncope, but there was little difference. Whether the atrioventricular block was constantly present or intermittent, or whether the ventricular rate was below or above 40 did not influence mortality. Though the mortality of women is lower than that of men in the general population, in the age groups considered, a similar mortality ratio between the two sexes was seen in the paced series.

It was hoped that analysis of the electrocardiogram before pacing was instituted might give some indication of prognosis but there was no significant difference when we analysed groups consisting of complete heart block with an idioventricular rhythm of right bundle-branch block type, complete heart block with a QRS of 0·1 s or less, or

Table 2 *Electrocardiographic findings related to long-term prognosis**

	No. of patients	*Actual deaths*	*Expected deaths*	*Mortality ratio*
Complete block with RBBB	437	150	94·8	1·6:1
Complete block with LBBB	151	49	30·8	1·6:1
Complete block QRS 0·1 s or less	99	26	16·3	1·6:1
Complete block QRS more than 0·1 s	640	225	134·6	1·7:1
Complete block with LAD	324	120	68·6	1·8:1

*Of the 839 patients reviewed in this series the prepacing electrocardiogram was not available for analysis in 61 patients and 39 patients had normal conducted sinus rhythm.

Table 3 *Mortality in 128 unpaced patients*

Age when first seen (y)	*No. of patients*	*Actual deaths*	*Expected deaths*	*Mortality ratio*
50-69	67	30	7·3	4·1:1
70-89	61	37	15·4	2·4:1

complete heart block with left axis deviation (Table 2).

The most important correlations were found when analysing the age groups paced (Table 1). These figures suggest that patients between the ages of 80 and 89 years when paced can expect to live as long as others of the same age and sex without heart block. There was, however, a very high mortality ratio of 4·5:1 for the 90 patients in the age group 50 to 59 years. This higher mortality ratio was also apparent in the very much smaller series of unpaced patients (Table 3). This analysis was based on 128 patients observed unpaced for a minimum period of 6 months. Of the 128 patients, 52 were subsequently paced and are thus included in both the unpaced and paced series.

Discussion

The higher mortality in the first year of pacing compared with subsequent years is similar to that reported by Sowton (1967) and Edhag (1969) and is largely the result of underlying myocardial or coronary disease, the complications of the surgical procedure, and sudden death sometimes known to be caused by ventricular fibrillation; it also includes a few deaths from technical failure of the pacing system. In addition, the high mortality in the early years of our pacing experience (before 1965) is similar to that of others when pacing was undertaken by the epicardial route. A detailed study of reports from this period suggests that a significant number of deaths were directly related to thoracotomy and were the result of chest complications and postoperative sepsis. Our own postoperative mortality with methods using thoracotomy was 8 in 59 patients (Harris *et al.*, 1965) as opposed to 1 in 49 patients with pacemaker implants associated with endocardial electrodes (Bluestone *et al.*, 1965).

Since a proportion of deaths are sudden despite pacing, we reviewed a variety of prepacing features including syncope, previous myocardial infarction, heart failure, and the electrocardiographic appearances in relation to eventual prognosis. As noted by Cosby *et al.* (1965) the presence or absence of previous myocardial infarction was the critical factor in determining prognosis and none of the other clinical or electrocardiographic indices were significantly related to long-term survival.

The most interesting feature of this study was revealed when survival was correlated with the age at which the patient was first paced. During the course of follow-up, in the group as a whole, approximately 1 in 3 patients had died irrespective of the age when first paced (Table 1). The poor prognosis of the patients under 60 years only becomes apparent when compared with patients of the same age in the general population without heart block. The relatively poor prognosis in the younger patient paced for complete heart block is presumably the result of the presence of additional heart disease such as coronary artery disease or congestive cardiomyopathy, whereas in the older patient heart block is commonly associated with idiopathic bundle-branch fibrosis without additional cardiac pathology (Davies, 1971).

Previous reports from our group have shown how difficult it is in life to determine the aetiology of atrioventricular block because once left bundle-branch block or complete heart block has developed the electrocardiogram is usually unhelpful (Harris *et al.*, 1969; Chatterjee *et al.*, 1970). In a recent communication (Siddons, 1974) we have analysed the causes of death in 145 long-term paced patients: 33 per cent of deaths were attributed to cardiovascular complications such as congestive heart failure, myocardial infarction, and cerebrovascular accidents; in 31 per cent of cases death was the result of unrelated causes such as malignancy and pneumonia; late sudden death occurred in 23 per cent of patients, and death was attributed to pacing in 8 per cent of the series. Unfortunately standard necropsy procedures rarely provide definite evidence of the aetiology of atrioventricular block or of the mechanisms of death. A detailed necropsy including coronary angiography and a study of serial sections of the conducting tissue has been carried out in

130 patients at our institution paced for chronic atrioventricular block (M. J. Davies, 1978, personal communication). The pathology of the underlying atrioventricular block was considered to be a result of idiopathic bundle-branch fibrosis in 43 per cent of cases; 24 per cent of patients had severe coronary artery disease, and block was associated with diffuse cardiomyopathy in 11 per cent of cases. The incidence of coronary artery disease as a cause of death in paced chronic heart block varies widely. Robboy *et al.* (1969) recorded 7 necropsies, in 3 of which acute myocardial infarction was considered the cause of death. Donmoyer *et al.* (1967) reported 17 deaths, 4 of which were attributable to myocardial infarction with necropsy confirmation in 3. Edhag (1969) reviewed the mode of death in 62 of 260 patients paced for complete heart block. Myocardial infarction was shown at necropsy in 23 (44%) of the 52 patients coming to necropsy, and infarction was estimated to be less than 2 weeks old in 17 of the 23 patients.

Although we are uncertain at the present time as to the cause of the high mortality ratio in patients paced for complete heart block in middle age, the increased risk of death may reflect a higher incidence of ischaemic heart disease as the cause of the atrioventricular block and this possibility needs further investigation. When considering the prognosis of paced chronic heart block it is therefore important to consider the age group involved. For those patients who have none of the adverse features, that is those who are aged 60 to 89 years, first paced after 1965, and with no previous history of myocardial infarction, the expectation of life if paced does not differ from that of the general population of the same age and sex without heart block.

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British Heart Journal, 1979, **41**, 637-646

Complete right bundle-branch block

Echophonocardiographic study of first heart sound and right ventricular contraction times

NICHOLAS BROOKS[1], GRAHAM LEECH[2], AND AUBREY LEATHAM

From St George's Hospital, London

SUMMARY High speed echocardiograms of the mitral, tricuspid, and pulmonary valves were recorded with a simultaneous electrocardiogram and phonocardiogram in 20 patients with complete right bundle-branch block and in 67 normal subjects. Late opening of the pulmonary valve indicating late right ventricular ejection was found in all patients. In 8 patients with wide splitting of the first heart sound the late ejection was related mainly to delay in tricuspid valve closure, suggesting a late onset of the right ventricular pressure pulse. In 10 patients with a single first heart sound the delayed ejection was associated with a long interval between tricuspid valve closure and pulmonary valve opening, suggesting a slow rising right ventricular pressure pulse; 3 of these patients also had late tricuspid valve closure but the tricuspid component of the first sound was absent. Late onset of pressure rise is thought to result from block in the main right bundle-branch, and a slow rising pulse from block in the distal Purkinje network. These findings explain the conflicting results in previous studies of the first heart sound and right ventricular pressure pulse in patients with right bundle-branch block, and may have prognostic significance.

The finding of right bundle-branch block as an isolated electrocardiographic abnormality raises difficult prognostic problems, particularly in aviation and life assurance medicine, since the pathological basis and risk of progression to complete atrioventricular block are unknown. Differentiation of proximal block caused by disruption of the main bundle-branch, from peripheral (arborisation) block in which the disruption is in the distal Purkinje network, might well have considerable significance, but cannot be made on the electrocardiogram (Oppenheimer and Rothschild, 1917; Wolferth and Margolies, 1935; Rosenman *et al.*, 1950; Alzamora-Castro *et al.*, 1953). An attempt has therefore been made to obtain this information by studying the effect of complete right bundle-branch block on contraction times. Cardiac catheterisation with catheter tip manometers and analysis of pressure pulses is seldom justifiable in subjects with isolated conduction disturbances, and the findings cannot be applied to patients with abnormal haemodynamics. Abnormally wide splitting of the second heart sound from late pulmonary valve closure is found in right bundle-branch block with a QRS duration of 120 ms or more (Haber and Leatham, 1965) and wide splitting of the first heart sound caused by delayed tricuspid closure should be a useful sign of a late onset of the right ventricular pressure pulse. Identification of the components of the first sound is sometimes uncertain however, and furthermore the isovolumic contraction period and moment of ejection cannot be recorded in the absence of an ejection sound.

High resolution echophonocardiography which permits exact timing of mitral and tricuspid valve closure and aortic and pulmonary valve opening (Leatham and Leech, 1975; Waider and Craige, 1975) can now be used to study mechanical events on each side of the heart. We report the use of this technique to analyse the mechanism of delay in subjects with complete right bundle-branch block in whom resting haemodynamics were thought to be normal.

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[1] British Heart Foundation Junior Research Fellow.

[2] British Heart Foundation Senior Research Fellow.

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Patients and methods

There were 20 patients aged 11 to 74 in whom electrocardiograms showed a slurred 's' wave in leads 1 and V7, and a secondary 'R' deflection in the right praecordial leads but in whom there was no evidence of pulmonary hypertension or cardiac failure. The QRS duration varied between 120 and 200 ms and the PR interval from 120 to 190 ms.

Sixty-seven normal volunteers, 27 men and 40 women aged 19 to 56, served as controls.

The subjects were studied with the trunk raised approximately 30 degrees and tilted to the left when this was necessary to obtain satisfactory recordings. The echocardiogram was recorded on a Smith Kline ultrasonoscope using a 2·25 MHz focused transducer with pulse repetition frequency increased to 2000/s. The output was displayed on a Cambridge six-channel recorder modified to improve echo depth magnification and with maximum paper speed increased to 200 mm/s. The standard lead electrocardiogram showing the earliest QRS onset was recorded simultaneously, together with a high frequency phonocardiogram from the lower left sternal edge unless it interfered with placement of the echo transducer in which case it was recorded separately. All recordings were made with maximum magnification of the echo display and at a paper speed of 200 mm/s.

The mitral valve was identified by the standard technique and recorded to show its moment of closure, defined as the point of complete apposition of the anterior and posterior cusps. The ultrasound beam was then angled medially to identify the characteristic movement of the anterior leaflet of the tricuspid valve. In order to visualise the point of cusp apposition, however, it is necessary to direct the transducer inferiorly until nearly all of the anterior leaflet echoes have disappeared. This manoeuvre usually enables a small part of both the anterior and posterior leaflets to be visualised as they meet and form the systolic closure line. The typical appearance is shown in Fig. 1. Sometimes two cusps cannot be visualised at the same time and in such cases we have found that the best definition of valve closure is obtained from the posterior (septal) cusp which shows a sharply defined 'shoulder' as it abruptly changes direction. Fig. 2 is the tricuspid valve echo from the same subject as Fig. 1 and shows this appearance. Note that in both views valve closure coincides exactly with the beginning of the second high frequency component of the first heart sound (T1). Finally, the posterior pulmonary valve cusp was located by pointing the transducer superiorly and laterally from the aortic root position, and a recording was made to show the full extent of its opening movement.

Whenever possible recordings were made in shallow held expiration (taking care to prevent the patient from performing a Valsalva manoeuvre), but in a number of cases the points of interest on the echocardiogram were visible only during other phases of the respiratory cycle. We have, however, made a number of recordings during continuous respiration and, surprisingly, the timing of mitral and tricuspid closure and complete pulmonary opening do not vary appreciably in normal subjects.

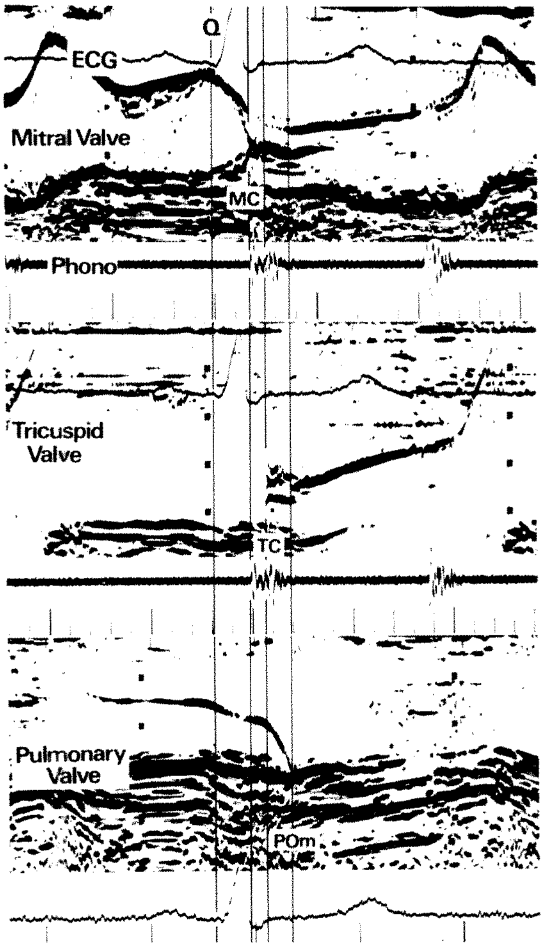

Fig. 1 *Echocardiograms of the mitral, tricuspid, and pulmonary valves with a simultaneous electrocardiogram and phonocardiogram from a normal subject. The recordings have been aligned on the Q wave of the electrocardiogram to illustrate the measurements. MC, mitral valve closure; TC, tricuspid valve closure; POm, complete pulmonary valve opening; time lines, 40 ms.*

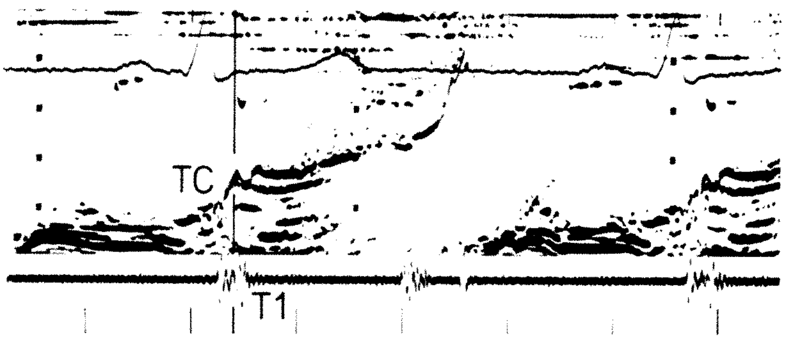

Fig. 2 *Tricuspid valve echocardiogram with simultaneous phonocardiogram from the same subject as in Fig. 1, but showing only the posterior valve cusp at the point of closure.*

Table 1 *Results*

Normal subjects	*Q-MC (ms)*	*Q-TC (ms)*	*MC-TC (ms)*	*Q-POm (ms)*	*TC-POm (ms)*
Mean	54·5	87·0	33·8	126·4	38·6
Standard deviation	11·0	16·6	10·5	14·3	12·2
Standard error of mean	1·3	2·1	1·3	2·1	1·8
No.	67	63	63	47	46
Right bundle-branch block					
Group 1—Split S1					
(1) Isolated RBBB	60	126	66	175	49
(2) Isolated RBBB	80	140	60	203	63
(3) Isolated RBBB	58	117	59	161	44
(4) Isolated RBBB	70	125	55	178	53
(5) Closed VSD	64	119	55	160	41
(6) Closed ASD	66	136	70	189	53
(7) ? angina	60	120	60	185	65
(8) SA node disease	50	102	52	172	70
Means	63·5	123·1	59·6	177·9	54·8
Group 2—Single S1					
(9) Intermittent CHB	65	87	22	181	94
(10) Intermittent CHB	75	95	20	172	77
(11) Anterior infarct; LAD	50	70	20	160	90
(12) Angina; LAD; intermittent CHB	88	98	10	233	135
(13) Angina	84	118	34	186	68
(14) Mild AS; LAD	50	85	35	171	86
(15) Healed myocarditis	60	81	21	160	79
(16) Intermittent CHB; LAD	41	94	53	183	89
(17) LAD	53	135	72	210	75
(18) LAD ? cardiomyopathy	45	100	55	197	97
Means	61·1	96·3	34·2	185·3	89·0
Absent S1					
(19) Obese; ant. infarct; LAD	48	101	53	166	65
(20) Long PR; closed ASD; LAD	53	107	54	178	71

VSD, ventricular septal defect; ASD, atrial septal defect; CHB, complete heart block; LAD, left axis deviation; AS, aortic stenosis.

MEASUREMENTS

Time intervals were measured to the nearest 0·5 mm (equivalent to 2·5 ms) using a hair-line cursor on a special measuring device. A correction was made for variations in paper speed by measuring the time between six 0·2 s markers. If electrocardiographic noise made it difficult to identify the q wave in an individual beat, measurements were made from the R wave and the q to R time was added. In each recording 5 cardiac cycles were averaged. The following intervals were measured:

(1) Onset of the initial deflection of the QRS complex of the electrocardiogram to mitral valve closure (Q-MC).
(2) Onset of QRS to tricuspid valve closure (Q-TC).
(3) Onset of QRS to maximal opening of the pulmonary valve (Q-POm).

The onset of pulmonary opening was not used for measurement because it is impossible to define this point precisely when only one valve cusp can be visualised. For this reason the point of complete opening was taken. This is often marked by a definite 'shoulder' at which point its posterior movement is arrested and the cusp begins to move in an anterior direction. When this shoulder was not seen the full posterior extent of the pulmonary valve echo was used.

Q-MC was subtracted from Q-TC to give the interval between mitral and tricuspid valve closure (MC-TC), and Q-TC from Q-POm to derive the interval from tricuspid closure to pulmonary opening (TC-POm). The estimation of these intervals is illustrated in Fig. 1 which is a set of recordings from a subject with normal intraventricular conduction.

Results

(1) 67 NORMAL SUBJECTS

The mean Q-MC, Q-TC, MC-TC, Q-POm, and TC-POm intervals in the normal subjects are summarised in Table 1, and the mean and normal ranges (mean ± twice the standard deviation) of

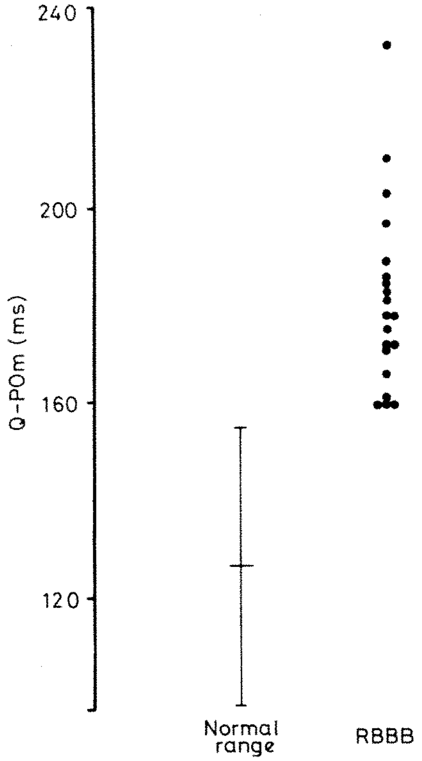

Fig. 3 *The timing of pulmonary valve opening in patients with right bundle-branch block compared with the normal range (mean ± 2 standard deviations).*

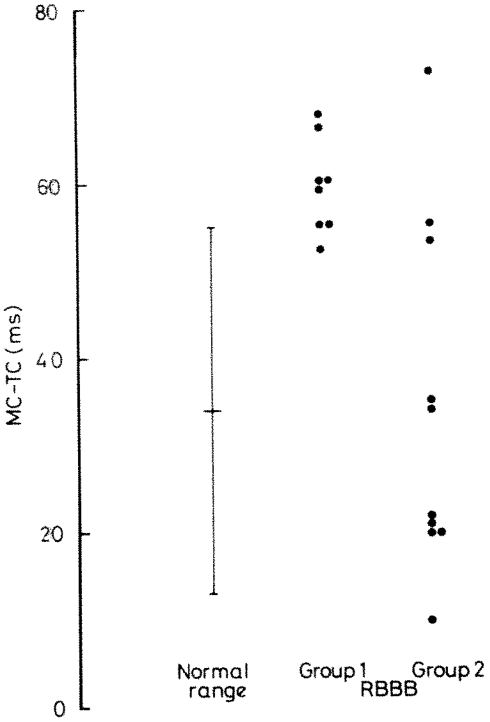

Fig. 4 *MC-TC in the two groups of patients with right bundle-branch block in comparison with the normal range.*

Q-POm, MC-TC, and TC-POm are shown in Fig. 3, 4, and 5. There was no significant correlation between MC-TC and the PR interval.

In all subjects with a PR interval of less than 180 ms the onset of the first high frequency component of the first heart sound coincided exactly with mitral valve closure on the echo. Whenever tricuspid valve closure was more than 20 to 30 ms after mitral closure, it occurred synchronously with a second high frequency component (T1). At shorter MC-TC intervals it was not possible to distinguish two separate components of the sound. At PR intervals longer than 180 ms the first sound was often absent or represented solely by vibrations coincident with tricuspid closure. These findings will be reported in detail elsewhere.

(2) 20 PATIENTS WITH COMPLETE RIGHT BUNDLE-BRANCH BLOCK

Pulmonary valve opening

Complete pulmonary valve opening was delayed in the patients with right bundle-branch block. The Q-POm interval exceeded two standard deviations above the normal mean in every case and the mean value was 181·0 ms, 55 ms longer than normal. These findings are illustrated in Fig. 3.

Timing of tricuspid valve closure

The timing of tricuspid valve closure can be assessed from either the MC-TC or from the Q-TC interval. Mean MC-TC was 46·3 ms, which is only 12·5 ms longer than the mean value in the normal subjects, but individual results ranged widely from 10 to 70 ms. Similarly, the mean Q-TC interval was 107·8 ms, 20·8 ms longer than normal and ranged from 70 ms (well within the normal range) to 140 ms (20 ms above the upper limit of normal).

Interval from tricuspid closure to pulmonary opening

The mean TC-POm interval was 73·2 ms, which is 34·6 ms longer than the mean value of the control subjects, a difference that is highly significant ($P < 0{\cdot}01$), but as with the timing of tricuspid closure there was considerable individual variation from those well within the normal range up to those 72 ms above its upper limit.

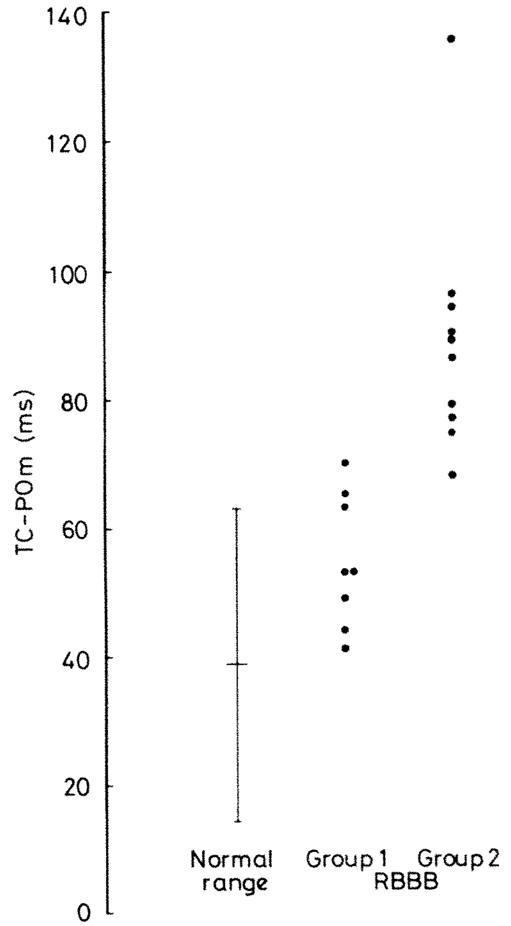

Fig. 5 *TC-POm in the two groups of patients with right bundle-branch block in comparison with the normal range.*

First heart sound

In 8 patients the first heart sound was widely split. This was easily detected by auscultation and confirmed by the phonocardiogram. Ten patients had a single first sound and the echophonocardiogram showed that this began at the moment of mitral valve closure. In 5 of these patients tricuspid closure followed mitral closure by more than 30 ms but did not produce an audible or recordable sound. One patient (case 20) had no detectable first sound in association with a long PR interval and in another the sound was muffled by obesity.

It was very striking that all 4 patients with right bundle-branch block and no other evidence of cardiovascular disease ('isolated right bundle-branch block') had a widely split first sound while the finding of a single first sound was in most cases associated with evidence of more extensive disease of the conducting system. We divided the patients into two groups on the basis of their first sounds: group 1 consisted of 8 patients with a widely split first sound and group 2 of 10 patients with a single sound. The echocardiographic time intervals were then compared.

Q-POm

Mean Q-POm in group 1 was 177·9 ms and in group 2 it was 185·3 ms. The difference between the two groups is not statistically significant ($P > 0{\cdot}20$).

Q-TC and MC-TC

Mean Q-TC in group 1 was 123·1 ms. This is significantly longer than both the group 2 value of 96·3 ms and the normal mean of 87·0 ms ($P < 0{\cdot}01$ in both cases). The difference between group 2 and the normals is not significant.

Mean MC-TC in group 1 was 59·6 ms: this too is significantly longer than the normal subjects (33·8 ms) and group 2 (34·2 ms) at the 1 per cent level. The small difference between the normals and group 2 could have arisen by chance.

The individual MC-TC intervals are shown in Fig. 4. Though the mean value for group 2 was not significantly different from normal, it can be seen that the interval exceeded, or was very close to the upper limit of the normal range, in 3 patients (cases 16, 17, and 18). In cases 16 and 18 this delay in tricuspid closure was not apparent when timed from the electrocardiographic Q wave (Q-TC).

Interval from tricuspid closure to pulmonary opening

The mean TC-POm interval was 54·8 ms in group 1 and 89·0 ms in group 2. The difference between groups 1 and 2, and between both patient groups and the normal subjects was highly significant ($P < 0{\cdot}01$ in all cases). In other words the longest mean TC-POm was in group 2 but that for group 1 was also significantly longer than normal. These results are shown in Fig. 5.

SUMMARY OF RESULTS

The findings in the two clinical groups may be summarised as follows (Table 2):

Table 2

	First sound	*Pulmonary opening*	*Tricuspid closure*	*Tricuspid closure to pulmonary opening*
Group 1	Wide split	Late	Late	Slightly long
Group 2	Single	Late	Normal or late	Long

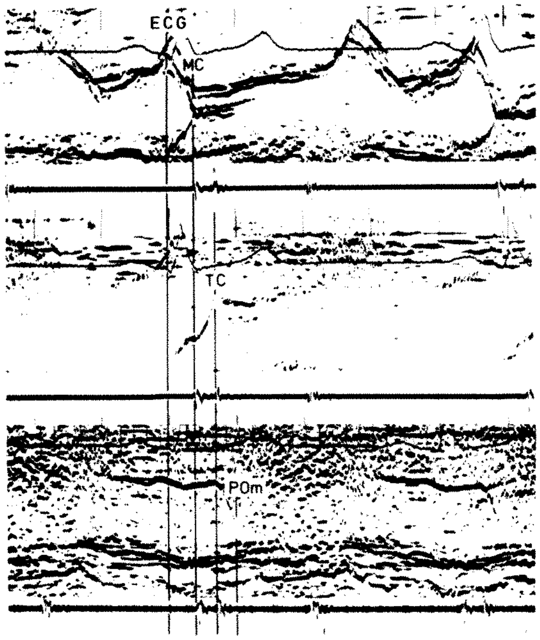

Fig. 6 *Echo and phonocardiograms displayed as in Fig. 1 from a patient in group 1 (case 2) with isolated right bundle-branch block. Tricuspid closure is late, the first sound widely split, and the TC-POm interval slightly longer than normal.*

The results from the 2 patients with inaudible first sounds are given in Table 1. In both the MC-TC interval exceeded 50 ms and TC-POm was above the normal range.

Typical echo and phonocardiograms are illustrated in Fig. 6, 7, and 8.

CLINICAL DETAILS

In 4 of the group 1 patients right bundle-branch block was the only abnormal finding ('isolated right bundle-branch block'). Two patients, cases 5 and 6, had surgically corrected congenital heart disease; in both the right bundle-branch block was present before operation. Case 8 had sinuatrial node disease and case 7 had atypical chest pain thought possibly to be angina.

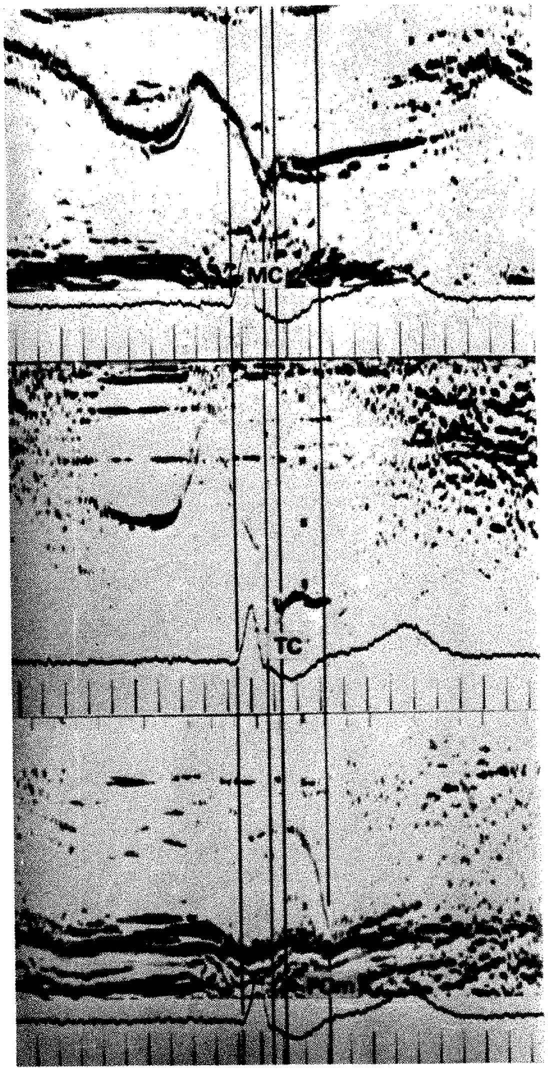

Fig. 7 *Echocardiograms displayed as in Fig. 1 from a patient in group 2 (case 11). Tricuspid valve closure is at the normal time (MC-TC = 20 ms) but the TC-POm interval is prolonged.*

None of the group 2 patients had right bundle-branch block as an isolated finding. Four had episodes of intermittent complete heart block; during conducted rhythm 2 of these had right bundle-branch block and a normal frontal plane QRS axis and 2 had left axis deviation consistent with a diagnosis of additional left anterior hemiblock. Four other patients also had right bundle-branch block with left anterior hemiblock. Case 13 had angina pectoris. Case 15 developed right bundle-branch block during a presumed viral myocarditis 2 years before; at the time of study there was no evidence of residual heart muscle damage. Case 18 had multiple ventricular extrasystoles and was suspected of having a cardiomyopathy, though resting intracardiac pressures were normal and the left ventricular angiogram showed no evidence of a contraction abnormality.

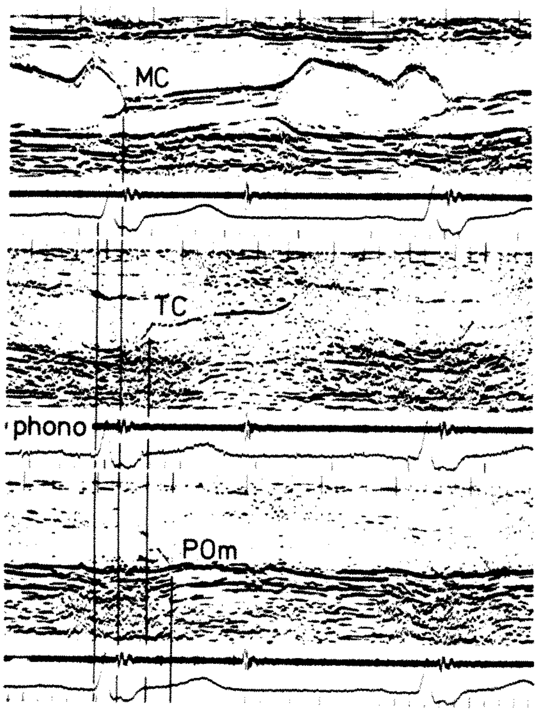

Fig. 8 *Echo and phonocardiograms displayed as in Fig. 1 from a patient in group 2 (case 17) with right bundle-branch block and left axis deviation. Tricuspid closure is late (long Q-TC and MC-TC) and TC-POm is lengthened. Despite the late tricuspid closure the first sound is single because T1 is absent.*

Discussion

The mechanical effects of bundle-branch block and their relation to pathological changes in the intraventricular conducting system have been studied for many years. In left bundle-branch block ejection from the left ventricle begins late, in most cases because of prolongation of the isovolumic contraction period, with little or no delay in the onset of contraction (Coblentz *et al.*, 1949; Braunwald and Morrow, 1957; Bourassa *et al.*, 1962; Haber and Leatham, 1965; Adolph *et al.*, 1969). This is consistent with the concept of arborisation block, with the implication that the pathological changes are located in the distal Purkinje network and the main bundle is at least partially intact. Such changes would lead to slow spread of activation through the ventricular myocardium, a reduced rate of pressure development, and consequent lengthening of the isovolumic contraction period.

In right bundle-branch block the invariable delay of the pulmonary component of the second heart sound indicates late termination of right ventricular systole, but there is controversy over the cause of this delay. Leatham and Gray (1956) observed a late onset of the right ventricular pressure pulse and of the tricuspid component of the first heart sound in 6 patients with atrial septal defect and complete right bundle-branch block (but not with incomplete right bundle-branch block) and this was supported by a phonocardiographic study (Haber and Leatham, 1965) in which wide splitting of the first sound (caused by a late tricuspid component) was observed in another group of patients with this conduction disturbance and also with ectopic beats thought to arise from the left ventricle. While observations on heart sounds strongly suggested that tricuspid valve closure, and therefore the onset of the right ventricular pressure pulse, was late in right bundle-branch block, the origin of this sound could not be proved and indeed the whole concept of valve closure as the cause of heart sounds has been challenged (Luisada, 1975). Furthermore, some studies of right bundle-branch block showed absence of delay in some cases (Braunwald and Morrow, 1957). Echocardiograms with simultaneous phonocardiograms, however, showed a loud late component of the first sound coinciding exactly with the final halt of the closing tricuspid valve in Ebstein's anomaly with right bundle-branch block (Crews *et al.*, 1972) and high speed, high definition echocardiography has now established that the initial high frequency component of the first sound coincides with mitral closure and the second component with tricuspid closure (Leatham and Leech, 1975; Waider and Craige, 1975): the normal interval was found to be 30 ms (Waider and Craige, 1975) which agrees with the 33·8 ± 1·3 ms (mean ± standard error) found in the present study.

Atrioventricular valve closure is normally initiated by atrial contraction and completed by ventricular contraction. A consequence of this is that the timing of mitral and tricuspid valve closure (relative to the onset of electrical depolarisation or ventricular contraction) is determined mainly by the PR interval. Mitral closure occurs before the onset of left ventricular contraction when the PR interval exceeds about 180 and 200 ms (Zaky *et al.*, 1969; Shah *et al.*, 1970; Burgraff and Craige, 1974); such presystolic closure is usually silent. In a recent study (Brooks *et al.*, 1978) we showed a comparable influence of PR interval on the timing of tricuspid closure, but the effect is weaker than on the mitral valve and presystolic closure does not seem to occur in normal subjects with PR intervals less than 220 ms. MC-TC however was found to be independent of PR interval changes up to about 190 ms, because the effects on the two valves largely cancel out. A major factor influencing MC-TC is believed to be the time relation between the onset of contraction of the left and right ventricles. From this we conclude that in the group 1 patients and cases 16, 17, and 18 in group 2 the long MC-TC interval is the result of delay in the onset of right ventricular contraction relative to the left, and that in the group 2 patients with normal MC-TC intervals right ventricular contraction begins at the normal time.

The relation of the echo measurement of tricuspid closure to pulmonary valve opening with the early phase of right ventricular contraction must now be discussed. Right ventricular ejection begins at the moment the pulmonary valve starts to open. Therefore the period from tricuspid closure to the onset of pulmonary opening represents the later part of the isovolumic contraction period. By analogy with the left ventricle, the isovolumic contraction period depends on preload, afterload, contractility, and heart rate. In the patients in this study haemodynamics and therefore loading conditions were thought to be normal. No allowance was made for heart rate but there were no extreme variations in either the control or patient groups. Changes in the period from tricuspid closure to onset of pulmonary opening must therefore result mainly from alterations in the rate of right ventricular pressure development (dP/dT). The period from onset to full opening of the pulmonary valve occurs during the early phase of ejection and it seems reasonable to assume that the time taken for full opening reflects the initial acceleration of blood flow in the pulmonary artery. Provided impedance to ejection is constant this time would also be determined by dP/dT. Thus it may be concluded that under the conditions of this study changes in TC-POm reflect mainly alterations in the rate of pressure development in the right ventricle.

However, since atrioventricular conduction time affects the timing of tricuspid valve closure (Q-TC) it must also influence the TC-POm interval. In the group 1 patients right ventricular contraction is thought to begin late in which case the time between activation of the right atrium and the right ventricle must be longer than in a normal subject with the same PR interval. The tricuspid valve leaflets will be more closely apposed when right ventricular contraction begins than if contraction had started at the normal time and closure will be completed earlier after the onset of pressure rise than normal. It would be expected therefore that Q-TC and MC-TC would be prolonged by rather less than the delay in the onset of ventricular contraction, and that the difference would be reflected by a slight increase in TC-POm. The findings in group 1 are entirely consistent with this concept; pulmonary valve opening was delayed by an average of 51·5 ms, MC-TC by 25·8 ms, and TC-POm by 16·2 ms. In the group 2 patients, however, TC-POm was much longer, on average 50·4 ms more than normal—and this points to depression of right ventricular dP/dT presumably from uncoordinated contraction caused by the conduction disturbance.

Case 19 had indistinct heart sounds because of his thick chest wall, but the echocardiographic intervals —long MC-TC and TC-POm just over normal range—suggest that he has the type of mechanical disturbance believed to exist in the group 1 patients. In case 20 the inaudible first sound was associated with a long PR interval. Mitral closure may have occurred before the onset of left ventricular contraction so that MC-TC cannot reflect the asynchrony of ventricular contraction and it is not possible to assess the type of delay present.

In this study all the patients with right bundle-branch block had evidence of delayed ejection of blood from the right ventricle. It has been argued that there may be a different underlying mechanism in the two clinically distinguishable groups:

(1) Delayed onset of right ventricular contraction with a normal pressure upstroke indicated by a long MC-TC interval and slight lengthening of TC-POm.

(2) Slow rate of rise of right ventricular pressure indicated by a long TC-POm interval. In some of these patients MC-TC was also long, suggesting an additional delay in onset of right ventricular contraction.

Delayed onset of right ventricular contraction with a normal upstroke time suggests that the proximal part of the right bundle is blocked and that the Purkinje network is intact. These findings are comparable to experimental section of the right bundle (Braun-Menendez and Solari, 1937; Smith *et al.*, 1952). The interruption might be congenital in origin or the pathological change could be very localised. Slowing of the right ventricular pressure upstroke suggests diffuse damage to the distal Purkinje network; this can also be induced in the experimental animal (Abildskov *et al.*, 1965; Millar *et al.*, 1970) and its presence suggests more widespread disease.

In the first group with proximal block causing delay in tricuspid closure, wide splitting of the first heart sound caused by a late tricuspid component was present, enabling this diagnosis to be suspected from auscultation. In the second group with a slow rising ventricular pressure the tricuspid component of the first sound was inaudible. This is comparable to the soft mitral closure in left bundle-branch block (Haber and Leatham, 1965; Thompson *et al.*, 1975) and explains the discrepancies between previous studies of the first heart sound in right bundle-branch block (Haber and Leatham, 1965; Silie *et al.*, 1973). Thus wide splitting of the first heart sound in a patient with right bundle-branch block suggests that the block is proximal and, provided the PR interval is less than about 180 ms, a single first heart sound results from inability to hear tricuspid closure and favours arborisation block.

The number of patients so far investigated is small, but there is a striking dominance of widespread disease of the conducting tissue culminating in paroxysmal atrioventricular dissociation in group 2 patients thought to have arborisation block, compared with group 1 patients thought to have isolated proximal block, but a longer follow-up is required. In addition the findings in complete right bundle-branch block can be applied to some extent to the vexed problem of deciding the significance of an rSR complex in the right praecordial leads—so-called partial right bundle-branch block—with a QRS less than 120 ms duration. When associated with atrial septal defect, and therefore indicating right ventricular hypertrophy (Lasser *et al.*, 1951) there is no delay in the loud tricuspid component of the first heart sound and no delay in the onset of the right ventricular pressure upstroke (Leatham and Gray, 1956). The rSR complex usually reverts to normal after closure of the defect confirming that hypertrophy of the right ventricle was the cause. Yet this electrocardiographic pattern often seems indistinguishable from that caused by a minor conduction delay. In this case, however, abnormally wide splitting of the first heart sound caused by delay in the tricuspid component, confirmed by the echo finding of late tricuspid closure, points to a conduction defect rather than to right ventricular hypertrophy.

The work described is part of a study submitted by N.B. to the University of London for the degree of Doctor of Medicine.

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Patients treated in a coronary care unit without acute myocardial infarction

Identification of high risk subgroup for subsequent myocardial infarction and/or cardiovascular death

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SUMMARY Consecutive patients admitted to a coronary care unit (CCU) during one year were studied. The diagnosis of acute myocardial infarction was not substantiated by our criteria in 206 of the patients discharged from the CCU. Of these, 193 were retrospectively followed up during one year. Seventeen of the patients (9%) died from cardiovascular causes during the 1-year period. Another 14 patients (7 %) had a subsequent non-fatal acute myocardial infarction during the same period. The majority of the patients had coronary artery disease. Only 32 (17%) could be classified as non-coronary cases, and these had an excellent prognosis without any subsequent acute myocardial infarctions or deaths.

The occurrence of transient ST-T shifts in serial electrocardiograms obtained during the first 3 days in hospital selected a subgroup of patients who had a high risk for subsequent non-fatal acute myocardial infarction and/or cardiovascular death. This high risk subgroup provides a basis for more aggressive diagnostic and therapeutic intervention.

Increasing effort is made to identify patients at high risk for sudden death or acute myocardial infarction (Solomon *et al.*, 1969; Freeman and Loughhead, 1972; Helmers, 1974; Corday, 1977; Moss *et al.*, 1977; Vedin *et al.*, 1977; Vismara *et al.*, 1977). This is even more challenging since recent reports indicate the possibility of preventive measures (Ahlmark *et al.*, 1974; Wilhelmsson *et al.*, 1974; Multicentre International Study, 1975). Most studies in this field have been performed on patients with acute myocardial infarction (Ahlmark *et al.*, 1974; Helmers, 1974; Wilhelmsson *et al.*, 1974; Multicentre International Study, 1975; Moss *et al.*, 1977; Vedin *et al.*, 1977). However, in a recent study of patients admitted to a coronary care unit (CCU) with suspected acute myocardial infarction the diagnosis was unconfirmed by serial electrocardiograms and estimations of serum enzyme levels in 70 per cent. These patients had the same high risk of cardiovascular death as the patients discharged with a diagnosis of acute myocardial infarction with a 1-year and 2-year mortality of 10 and 20 per cent, respectively (Schroeder *et al.*, 1977). Therefore this study was undertaken with the aim of identifying a high risk subgroup for subsequent non-fatal acute myocardial infarction and/or cardiovascular death among the patients discharged from the CCU without a diagnosis of acute myocardial infarction.

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Subjects and methods

A consecutive series of patients admitted to the CCU of Huddinge Hospital from 1 January 1975 to 1 January 1976 was retrospectively studied. The admission criteria were: (1) central chest pain lasting for more than 15 minutes beginning within the previous 48 hours; (2) frank pulmonary oedema without previously known valvular lesion, uraemia, or intoxication; (3) shock without suspicion of acute hypovolaemia or intoxication; (4) syncope with electrocardiographic suspicion of acute myocardial infarction; (5) intractable angina pectoris. The criteria for a diagnosis of acute myocardial infarction was the fulfilment of a, b, or c below in addition to one of the admission criteria: (a) appearance of a pathological Q wave and/or appearance or disappearance of a localised pathological ST elevation followed by T inversion in at least 2 electrocardiographic leads in serial electrocardiograms;

(b) two serum AST (SGOT) values above the upper reference limit with a maximum about 24 hours after onset of symptoms in combination with lower serum ALT (SGPT) values; (c) findings at necropsy of a fresh myocardial necrosis. Patients partly fulfilling the criteria received a diagnosis of suspected acute myocardial infarction. This diagnosis was ruled out in patients not fulfilling any of the criteria a, b, or c. If a patient was admitted several times without a diagnosis of acute myocardial infarction only the first occasion was considered. All patients were clinically examined on admission and twice daily. Heart rate, respiratory rate, blood pressure, and arrhythmias were noted in a data chart.

A standard 12-lead electrocardiogram was obtained on admission and each morning during the following 3 days. Leads I, II, III, aVR, aVL, aVF, CR_4R, CR_1, CR_2, CR_4, CR_5, and CR_7 were used and the electrode positions were indicated on the chest wall by a marker pen to secure the same electrode positions in succeeding electrocardiograms. The electrocardiograms were recorded with a paper speed of 50 mm per second and with an amplification of 1 mV per 10 mm. A QRS duration over 0·12 s was defined as bundle-branch block. A transient ST shift was defined as an elevation or a depression of the ST segment of 1·5 mm or more compared with the preceding electrocardiogram regardless of the initial ST level. A transient T shift was considered when the T wave changed from a positive to a negative configuration or vice versa, regardless of the amplitude. The ST and/or T shifts should occur in at least 2 of the 12 electrocardiographic leads during the first 3 days. Serum AST (SGOT) and ALT (SGPT) were routinely analysed from samples obtained on admission and every day at 8 am and 8 pm for 3 days.

The patients were followed up after one year. The majority of them were periodically controlled as outpatients. Those not seen by us were traced and interviewed. Information was also obtained from private doctors and from records of other hospitals. Information about deaths was obtained from relatives, private doctors, and from the Government Institute for Forensic Medicine. Sudden death was defined as death occurring within 24 hours from onset of the acute illness. Instantaneous death was referred to as death occurring within minutes.

The significance of differences between mean values was tested by Student's t test. The χ^2 test with Yates' correction was used for testing the significance of differences of relative numbers. Differences with $P > 0{\cdot}05$ were considered not significant.

Results

During the 1-year period there were 187 patients with acute myocardial infarction and suspected acute myocardial infarction, but the diagnosis of acute myocardial infarction was not confirmed in 206 of the patients discharged from the CCU. A reliable follow-up could not be obtained in 13 patients (6%). Of the remaining 193 patients, 125 were men and 68 were women, with a mean age of 61 years, ranging from 30 to 89 years. Sixty-six patients (34%) had a history of previous myocardial infarction (Table 1). Fifty-four patients had a history of hypertension, 18 a history of diabetes mellitus, and 7 patients were treated for hyperlipaemia. One hundred and thirty-four patients (69%) had a history of angina pectoris. The duration of angina was 1 month or less in 13 cases and between 1 and 3 months in 4 cases.

During the CCU stay the following complications appeared (Table 2): Nine patients developed left heart failure, 3 patients hypotension and/or shock, 2 patients atrioventricular block I and/or II, 6

Table 1 *Previous diseases and mean age*

	All patients		*Cardiovascular deaths*		*Non-fatal acute myocardial infarction*		*Cardiovascular event*		*No cardiovascular event*	
	n = 193	*%*	*n = 17*	*%*	*n = 14*	*%*	*n = 31*	*%*	*n = 162*	*%*
Previous myocardial infarction	66	34	12	71***	9	64*	21	68***	45	28
Hypertension	54	28	4	24	4	29	8	26	46	28
Diabetes mellitus	18	9	5	29**	2	14	7	23*	11	7
Hyperlipaemia	7	4	1	6	1	7	2	6	5	3
Angina pectoris	134	69	15	88	13	93	28	90*	106	65
1 month	13	10	0	0	4	31	4	14	9	8
1-3 months	4	3	1	7	2	15	3	11	1	1
Mean age (y)	61		68*		60		64		61	

* $P < 0{\cdot}05$
** $P < 0{\cdot}01$
*** $P < 0{\cdot}001$
Statistical differences are calculated between subgroups and patients with no cardiovascular events.

Table 2 *Complications appearing in CCU*

	All patients		*Cardiovascular deaths*		*Non-fatal acute myocardial infarction*		*Cardiovascular event*		*No cardiovascular event*	
	n = 193	*%*	*n = 17*	*%*	*n = 14*	*%*	*n = 31*	*%*	*n = 162*	*%*
Left heart failure	9	5	3	18	0	0	3	10	6	4
Hypotension/shock	3	2	0	0	0	0	0	0	3	2
AV block I/II	2	1	0	0	0	0	0	0	2	1
Atrial fibrillation/flutter	2	1	0	0	0	0	0	0	2	1
Ventricular tachycardia	10	5	3	18	1	7	4	13	6	4

patients sinus bradycardia, 2 patients atrial fibrillation or flutter, and 10 patients ventricular tachycardia. The mean stay in the CCU was 24 hours and in the hospital 6 days.

During the 1-year follow-up 31 patients had at least 1 cardiovascular event. Twenty-three patients had acute myocardial infarction. Four of these died, 2 from sudden death, 1 from cardiogenic shock, and 1 from severe left heart failure. Of the remaining 19 hospital survivors there were 5 subsequent deaths without clinical or necropsy evidence of reinfarction. Three of these deaths occurred suddenly and 2 were the result of severe left heart failure. Eight patients died without evidence of acute myocardial infarction during the follow-up period, 5 from sudden death and 3 from severe left heart failure. Altogether there were 17 cardiovascular deaths and 14 patients with a non-fatal acute myocardial infarction (Fig. 1).

CARDIOVASCULAR DEATHS

Ages in this group varied between 47 and 85, mean 68 years. Previous diseases, physical findings on admission, and complications appearing in the CCU are shown in Tables 1 and 2. Seven (41%) of the 17 cardiovascular deaths occurred within 3 months and 11 (65%) within 6 months. Ten patients died suddenly, 4 of them instantaneously. Seven patients died from pump failure. Necropsy was performed in 12 cases.

NON-FATAL ACUTE MYOCARDIAL INFARCTION

Ages in this group varied between 45 and 75, mean 60 years. Previous diseases, physical findings on admission, and complications appearing in the CCU are shown in Tables 1 and 2. Non-fatal acute myocardial infarctions were more often associated with a history of previous myocardial infarction. Nine (64%) occurred within 3 months. The acute myocardial infarctions were diagnosed in hospital by enzymes and/or electrocardiogram in all patients but one. This outpatient's electrocardiogram showed fresh pathological Q waves in several leads of the anterior wall.

There were no significant differences in complications appearing in the CCU, maximal AST (SGOT) values or maximal AST (SGOT) change between patients with cardiovascular deaths, patients with non-fatal acute myocardial infarctions, and patients without any cardiovascular event.

Three patients were operated upon with coronary artery bypass surgery because of intractable angina pectoris and all survived without a subsequent acute myocardial infarction during the follow-up period.

ELECTROCARDIOGRAPHIC ABNORMALITIES

Of the 193 patients, 7 had left bundle-branch block, 6 had right bundle-branch block, 1 had pre-excitation, and 2 had pacemaker electrocardiograms. Of these 16 patients, 3 died, 2 with left bundle-branch block and 1 with right bundle-branch block. None had a non-fatal acute myocardial infarction. These patients were significantly older than the rest of the patients, 70 versus 61 years.

Among the remaining 177 patients there were

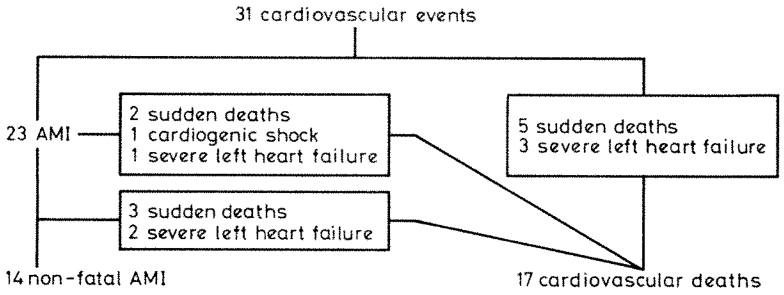

Fig. 1 *Cardiovascular events during the follow-up period.*

Table 3 *Transient ST-T changes in relation to cardiovascular events*

	ST-T changes *n = 36*	*No ST-T changes* *n = 141*	*Not possible to evaluate* *n = 16*	*P*
Cardiovascular event	19	9	3	< 0·001
No cardiovascular event	17	132	13	< 0·001

36 (20%) with transient ST-T changes. Their mean age, 61 years, did not differ from that of patients without transient ST-T changes, mean age 61 years. Three had ST changes only, 21 T changes only, and 12 patients ST and T changes. The maximal ST-T change from the preceding electrocardiogram occurred in the second registered electrocardiogram in 23 cases and in the third electrocardiogram in the other 13 cases. Among the 15 patients with ST changes, 8 had ST depression and 7 ST elevation, and 6 of the latter were in the form of reduced ST depression from the first registered electrocardiogram. The maximal ST change varied between 1·5 and 4 mm, mean 1·9 mm, and was found in leads III and aVL in 1 case, CR_2 in 3 cases, and leads CR_4 and CR_5 in 5 cases.

Among the 33 patients with T changes, 3 changes were from negative to positive T wave and the rest developed inverted T waves. Five patients developed symmetrically inverted T waves. The rest had diphasic T waves, 20 with a positive-negative and 8 with a negative-positive configuration. The maximal change of the T amplitude varied between 1·5 and 17 mm, mean 6·7 mm, and was found in leads III in 3 cases, CR_2 in 8 cases, CR_4 in 16 cases, and CR_5 in 6 cases.

Among the 36 patients with transient ST-T changes there were 9 who died subsequently of cardiovascular causes and 10 who developed a non-fatal acute myocardial infarction, altogether 19 patients (53%) with cardiovascular events. Nine patients (6%) had a subsequent cardiovascular event without transient ST-T changes during the same follow-up period. Three patients with bundle-branch block, in whom the ST-T changes could not be evaluated, died during the follow-up period (Table 3). No difference in the incidence of subsequent cardiovascular event was found regarding the localisation of the maximal ST and/or T change, the maximal change of the ST and/or T amplitude, or the type of T wave, i.e. symmetrical, biphasic positive-negative, or biphasic negative-positive.

NON-CORONARY PATIENTS

Thirty-two patients (17%) had no history of either previous myocardial infarction, angina pectoris, hypertension, hyperlipaemia, or diabetes mellitus. These patients were significantly younger than the rest of the patients. Their ages varied between 30 and 75 years, mean 55 years. None of these patients, including 3 patients with acute pericarditis, showed transient ST-T shifts. All of them survived during the follow-up period and none had a non-fatal acute myocardial infarction. The prognosis in this group compared with the non-acute myocardial infarction patients and with the patients with acute myocardial infarction is shown in Table 4. Exclusion of these patients did not change any of the above-mentioned statistical differences between the different groups.

Discussion

Patients in the present study, admitted because of suspicion of an acute myocardial infarction but without a subsequent diagnosis of acute myocardial infarction, appear to run a high risk for cardiovascular death with a 1-year mortality of 9 per cent. The majority of the patients had coronary artery disease. Only 17 per cent could be classified as non-coronary cases, and they had an excellent prognosis without any deaths or subsequent myocardial infarctions.

In a recent study (Schroeder *et al.*, 1977) of patients admitted to the CCU with chest pain 70 per cent did not have an acute myocardial infarction, and of these 18 per cent was judged to have non-cardiac chest pain. Among patients with prolonged ischaemic chest pain and transient ST changes, without acute myocardial infarction, a 4 per cent 1-month and a 10 per cent 1-year mortality was

Table 4 *One year incidence of cardiovascular events for patients with acute myocardial infarction, patients with non-acute myocardial infarction and non-coronary patients discharged from CCU*

	Patients with acute myocardial infarction *n = 187*	*%*	*Non-acute myocardial infarction patients* *n = 193*	*%*	*Non-coronary patients* *n = 32*	*%*
Non-fatal acute myocardial infarction	27	14	14	7	0	0
Cardiovascular deaths	32	17	17	9	0	0
Cardiovascular events	59	32	31	16	0	0

found. If the non-coronary cases in the present study are excluded, a 1-year mortality of 11 per cent is found. This mortality is almost the same as that after acute myocardial infarction (Hofvendahl, 1971). Dussia *et al.* (1976) found that patients admitted to the CCU with a history typical of myocardial infarction appeared to have a comparable in-hospital mortality rate after 48 hours, a comparable 1-year mortality rate, and a comparable incidence of recurrent myocardial infarction during the first year, whether or not they developed confirmatory electrocardiographic or serum enzyme changes.

Ten (40%) of the 23 deaths that occurred in the material of Schroeder *et al.* (1977) were sudden (within 24 hours) and 13 were caused by acute myocardial infarction or its complications. A similar proportion of sudden death (59%) was also found in the present study. Recently clinical studies have reported a reduction in sudden death with the routine use of beta-adrenergic blocking agents in postinfarction patients (Ahlmark *et al.*, 1974; Wilhelmsson *et al.*, 1974; Multicentre International Study, 1975). These results provide a basis for therapeutic trials in the type of patients discussed in the present study, preferably in a selected high-risk subgroup.

In an earlier report, Lopes *et al.* (1974) were unable to identify the patients who died subsequently from cardiac causes when comparing serial ST-T changes, frequency of premature ventricular beats, episodes of ventricular tachycardia or fibrillation, and conduction defects during hospitalisation with those of the group who survived during the follow-up. However, in the present study a high-risk group could be selected by transient ST-T changes in serial electrocardiograms. The sensitivity of the ST-T changes might be improved by a more frequent electrocardiographic recording or by ST-T mapping.

Transient ST-T changes have often been reported in association with conditions regarded as severe myocardial ischaemia, such as unstable angina, impending myocardial infarction, intermediate coronary syndrome (Bertolasi *et al.*, 1974; Berndt *et al.*, 1975; Chahine, 1975; Cairns *et al.*, 1976; Alison *et al.*, 1978) and is sometimes included as a major or minor criterion of unstable angina (Bertolasi *et al.*, 1974; Berndt *et al.*, 1975; National Cooperative Study Group, 1976; Day *et al.*, 1977; Hultgren *et al.*, 1977).

Another explanation of the ST-T changes might be an acute myocardial infarction, which is either too small to be detected by conventional enzymes or its onset is too early before admission to allow an enzyme diagnosis. In the first case it is known that 10 to 20 per cent of patients admitted because of suspected acute myocardial infarction, but with a ruled-out diagnosis, have increases in enzyme levels within the normal range and a prognosis similar to true acute myocardial infarction (Säwe, 1972). However, this author did not report whether the enzyme increases were correlated to any ST-T changes. Furthermore, patients in the present study with ST-T changes did not have significantly different maximal AST (SGOT) values or change of AST activity. This diagnostic problem is now being studied prospectively by a more frequent sampling of enzymes as well as by a more sensitive and specific enzyme method (Lundin and Styrélius, 1978).

In the second case, analysis of LDH could have been of value but was not routinely used in the present study. However, patients with ST-T changes did not have a significantly longer delay between onset of symptoms and admission to the CCU than patients without these electrocardiographic abnormalities. The important clinical finding is that, whether these patients have had a small acute myocardial infarction or not, they constitute a high risk group.

Bodenheimer *et al.* (1977) investigated the pathophysiological significance of ST and T wave abnormalities in 21 patients with the intermediate coronary syndrome, characterised by recurrent chest pain at rest associated with significant new ST or T wave abnormalities, or both, and no new Q waves in the surface electrocardiogram at the time of open heart coronary bypass surgery. These patients did not have Q waves either in the intraoperative epicardial or postoperative surface electrocardiogram. In 7 patients, a transmural biopsy specimen was also obtained from the ischaemic area. All showed histologically normal myocardium without evidence of early inflammatory or necrotic tissue.

The form of the T wave also merits some interest. In situations of coronary insufficiency it has been described as a deep symmetrically inverted T—a so-called 'coronary T' (World Health Organization, 1970). In the present study only 5 patients (15%) had symmetrically inverted T waves while in the rest they were diphasic, an example of which is shown in Fig. 2.

In conclusion, patients admitted to the CCU because of suspected acute myocardial infarction but without a subsequent diagnosis of acute myocardial infarction have a high risk for cardiovascular death with a 1-year mortality of 9 per cent and a 1-year incidence of non-fatal acute myocardial infarction of 7 per cent. The majority of the patients had coronary artery disease. Only 17 per cent could

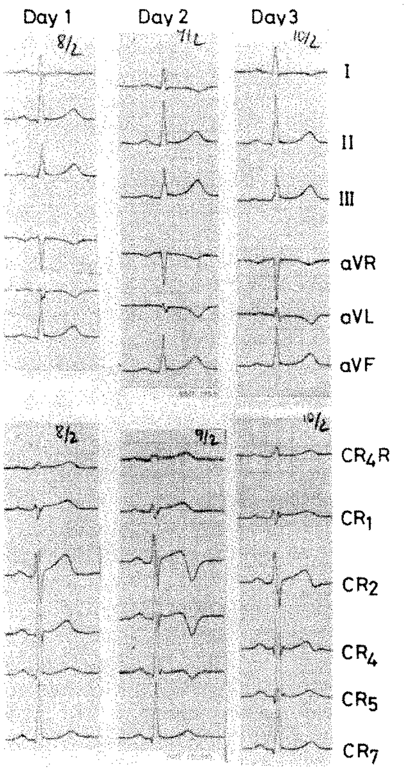

Fig. 2 *Example of transient ST-T changes.*

be classified as non-coronary cases, and they had an excellent prognosis without any deaths or subsequent acute myocardial infarctions. The occurrence of transient ST-T changes selected a subgroup of patients with a high risk for subsequent non-fatal acute myocardial infarctions and cardiovascular death. This high risk subgroup provides a basis for more aggressive diagnostic and therapeutic interventions.

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Reduction of early ventricular arrhythmia by acebutolol in patients with acute myocardial infarction[1]

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SUMMARY To assess the effects of intravenously administered acebutolol (1-20 mg every 4 hours for 24 hours) on cardiac rhythm and performance, we studied 72 patients with evolving myocardial infarction. Twenty-five patients were treated with acebutolol beginning 6 hours after the first increase in the level of plasma creatine kinase. Enzymatically estimated infarct size was compared with that of 25 controls matched for predicted infarct size. Observed infarct sizes were not significantly different in the 2 groups (37 ± 5 and 30 ± 5 CK-gram equivalents, respectively). Mean heart rate, diastolic blood pressure, and cardiac output declined from control values during treatment with acebutolol, but remained within the normal range. Mean pulmonary artery pressure and pulmonary artery occlusive pressure were unchanged. In a group of 22 treated patients matched with 22 control subjects for frequency of ventricular extrasystoles, acebutolol effected a prompt reduction in frequencies of ventricular extrasystoles and repetitive arrhythmias, whereas values were not significantly changed in controls during the corresponding intervals. Accordingly, acebutolol may be a useful antiarrhythmic agent in selected patients with acute myocardial infarction without adversely altering haemodynamic stability or enzymatically estimated infarct size.

Mortality during the acute phase of myocardial infarction is increased among patients with extensive myocardial necrosis (Page *et al.*, 1971) and among those with severe ventricular arrhythmias (Killip and Kimball, 1967). Though beta-adrenergic blockade appears to protect ischaemic myocardium (Maroko *et al.*, 1971) and exert favourable electrophysiological effects (Harris *et al.*, 1971) during ischaemia in experimental animals, administration of beta-adrenergic antagonists to patients with acute myocardial infarction has been tempered by the possible risk of precipitating heart failure. Acebutolol is a cardioselective beta-adrenergic antagonist with negative chronotropic effects particularly pronounced when circulating catecholamines are increased (Leary and Coleman, 1972). It alters airway resistance to a lesser extent than does propranolol (Kumana *et al.*, 1975) and is more effective than practolol in blocking tachycardia induced by isoprenaline (Cuthbert and Collins, 1975). Furthermore, acebutolol increases exercise tolerance and reduces both angina (Biron and Tremblay, 1976) and the frequency of ventricular extrasystoles in ambulatory patients with coronary artery disease (Gradman *et al.*, 1977). To evaluate the effects of this agent on ventricular arrhythmias, haemodynamics, and enzymatically estimated infarct size in patients with evolving myocardial infarction, we studied 25 patients treated with acebutolol and 2 groups of controls.

Methods

PATIENTS STUDIED AND ACEBUTOLOL PROCEDURE

Seventy-two subjects were studied after admission to the Cardiac Care Unit of Barnes Hospital with a diagnosis of acute myocardial infarction confirmed by characteristic history, electrocardiogram, and rise in plasma creatine kinase (CK) activity. Patients who had clinically evident bronchospasm or history of asthma, hepatic failure, renal failure, or uncontrolled diabetes mellitus were excluded. Acebutolol was administered to patients selected on the basis of heart rate exceeding 75 beats per minute, blood pressure exceeding 90/60 mmHg, and pulmonary artery occlusive pressure less than 20 mmHg.

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Of patients in this study, 25 were treated with acebutolol. Forty-seven acted as controls, since 2 control groups were necessary. One was a group of 25 matched with the treated patients on the basis of infarct size predicted before the onset of the intervention from an analysis of early plasma CK changes. The other control group comprised 22 patients matched with 22 treated patients for the frequency of ventricular extrasystoles before the administration of acebutolol. The arrhythmia-matched groups were smaller than those matched for predicted infarct size since Holter tapes covering the appropriate time intervals were not obtained in 3 patients treated with acebutolol. The comparability of control groups with treated patients is delineated in Tables 1 and 2.

Intravenous administration of acebutolol (1 to 20 mg every 4 hours for 24 hours) was initiated beginning 6 hours after the first rise in plasma CK activity. Dosage was adjusted to maintain heart rate between 60 and 75 beats per minute, pulmonary artery occlusive pressure below 20 mmHg, and systolic blood pressure above 90 mmHg.

QUANTIFICATION OF VENTRICULAR ARRHYTHMIA

The electrocardiograms of the 44 subjects, comprising treated patients and arrhythmia-matched controls, were continuously recorded for 15 hours after the initial increase in plasma CK activity. Holter tapes were analysed by the Argus/H computer system and checked visually (Nolle *et al.*, 1974). Both the incidence of ventricular extrasystoles and of repetitive arrhythmias (2 or more ventricular beats in a row) were evaluated.

Twenty-two subjects not treated with acebutolol were matched with the treated group on the basis of the number of premature ventricular complexes during the first 5 hours of recording since this interval immediately preceded the time of initial administration of acebutolol to the treated patients. The frequencies of ventricular extrasystoles and repetitive arrhythmias after the onset of treatment were compared with those during corresponding intervals after the first plasma CK rise in control subjects. In addition, differences in the frequency of ventricular arrhythmias before and during treatment in patients treated with acebutolol were compared with analogous differences in the control group. Student's t test was used to analyse the significance of differences between groups.

Lignocaine was administered intravenously as a 50 mg bolus or by continuous infusion to any patient when ventricular extrasystoles exceeded 10 a minute for 3 consecutive minutes or when couplets or ventricular tachycardia occurred. During the recording intervals similar amounts of lignocaine were required in control subjects and in those receiving acebutolol (1·67 ± 0·25 (SE) mg/min and 1·28 ± 0·21, respectively).

Table 1 *Initial characteristics of treated and control patients matched for predicted infarct size*

	Acebutolol (*n* = 25)	*Controls* (*n* = 25)
Age (y)		
Mean	59	62
Range	36-76	47-87
Sex (M:F)	16:9	20:5
Heart rate (beats/min)	83 ± 2	79 ± 3
Blood pressure (mmHg)		
Systolic	138 ± 5	139 ± 7
Diastolic	89 ± 3	85 ± 4
Predicted infarct size		
CK gram-equivalents	25 ± 4	25 ± 4

Note: Values for heart rate and blood pressure are those obtained during the one hour interval before administration of acebutolol, and during the corresponding interval in controls.

Table 2 *Initial characteristics of treated and control patients matched for premature ventricular complexes*

	Acebutolol (*n* = 22)	*Controls* (*n* = 22)
Age (y)		
Mean	59	62
Range	36-76	38-80
Sex (M:F)	14:8	15:7
Heart rate (beats/min)	83 ± 2	79 ± 4
Blood pressure (mmHg)		
Systolic	134 ± 5	142 ± 7
Diastolic	87 ± 4	82 ± 5
Ventricular extrasystoles, frequency	2·82 ± 0·43	2·76 ± 0·43

HAEMODYNAMICS

Heart rate and blood pressure were monitored non-invasively every 15 minutes in all patients for 24 hours. Serial determinations of pulmonary artery pressure, pulmonary artery occlusive pressure (indirect left atrial pressure recorded during inflation of balloon of Swan-Ganz catheter), and cardiac output measured by thermodilution method were made with the use of a Swan-Ganz catheter in patients treated with acebutolol. Haemodynamic measurements were obtained immediately before and after each dose and ½ hour, 1 hour, and subsequently every 2 hours after administration of the drug to assess haemodynamic response. Patients in the control groups were evaluated by invasive methods only when this was required for clinical management.

ENZYMATIC ESTIMATES OF INFARCT SIZE

Enzymatic estimates of infarct size in all 25 patients treated with acebutolol were compared with

Table 3 *Effects of acebutolol on ventricular arrhythmias*

Time (h)	*Acebutolol (n = 22)*		*Control (n = 22)*	
	Total ventricular extrasystoles	*Repetitive arrhythmias*	*Total ventricular extrasystoles*	*Repetitive arrhythmias*
0-5	2·82 ± 0·43	0·337 ± 0·15	2·76 ± 0·43	0·499 ± 0·17
6-10	2·11 ± 0·41	0·138 ± 0·10	2·81 ± 0·44	0·324 ± 0·15
11-15	1·89 ± 0·38	0·113 ± 0·06	1·99 ± 0·38	0·207 ± 0·09

Note: The values for arrhythmias in the 6 to 10 hours in the treated group (acebutolol) were significantly less than those observed during the initial 5 hours (P < 0·025) but no significant difference was seen during comparable intervals in the controls.

estimates in 25 control subjects matched for projected infarct size. Blood samples for serial determinations of plasma CK activity were obtained, stored, and analysed as described previously (Roberts *et al.*, 1975). Predicted infarct size was estimated from projected values conforming to the best fit log normal curve derived from plasma CK values during the first 6 hours after the initial rise (Shell *et al.*, 1973). Since acebutolol was not administered until data needed for projection of the log normal curve had been obtained, estimates of predicted infarct size were not influenced by the intervention. Observed infarct size was estimated from all serial plasma CK values during the first 72 hours after the initial increase or until values had returned to the normal range (Sobel *et al.*, 1977).

Results

EFFECTS OF ACEBUTOLOL ON VENTRICULAR ARRHYTHMIA

Results of analysis of rhythm are summarised in Table 3. Because the frequency of ventricular extrasystoles is not normally distributed, statistical treatment with conventional procedures such as Student's t test is not appropriate. However, when values of the frequency of ventricular extrasystoles are expressed as logarithms, the distribution of values conforms closely to a normal distribution. Accordingly, results of frequency of ventricular extrasystoles were expressed in terms of logarithmic values and were then analysed by Student's t test. In patients treated with acebutolol, the natural logarithm of the total number of ventricular extrasystoles decreased from 2·82 ± 0·43 (mean ± SE) during the initial 5-hour interval to 2·11 ± 0·41 (P < 0·001) during the 5 hours immediately after initiation of treatment, and did not change significantly during a subsequent 5-hour recording interval (1·89 ± 0·38). Similarly, the number of complex arrhythmias decreased from 0·377 ± 0·15 to 0·138 ± 0·10 (P < 0·05) during the 5 hours after the initiation of treatment and remained stable in the subsequent 5 hours (0·113 ± 0·06). In contrast, the frequency of ventricular extrasystoles among patients in the control group was unaltered from the first to the second 5-hour interval (2·76 ± 0·43 versus 2·81 ± 0·44, respectively). Furthermore, the incidence of repetitive arrhythmias (Table 3) which was not significantly different from that of the treated patients during the first 5 hours (P > 0·35) did not decline significantly during the second 5 hours (0·499 ± 0·17 versus 0·324 ± 0·15, respectively, P > 0·20). Thus, administration of acebutolol effected a prompt reduction in the frequency of ventricular extrasystoles and of repetitive ventricular arrhythmias in patients with acute myocardial infarction.

HAEMODYNAMICS

The results of haemodynamic determinations are summarised in Table 4. As expected, the mean heart rate of patients treated with acebutolol decreased from 83 ± 2 (SE) beats per minute to 71 ± 1 (P < 0·05) during administration of the drug. In contrast, the mean heart rate of the control group did not change during the corresponding interval (79 ± 3 compared to 81 ± 3 beats per minute). Mean systolic and diastolic blood pressures were similar initially in both groups and showed equivalent modest declines. Mean pulmonary artery occlusive pressure was unchanged from pretreatment values by administration of the drug but cardiac output declined from 5·0 ± 0·2 (SE) to 4·5 ± 0·3 l/min, consistent with a decrease in heart rate.

In 2 patients treated with acebutolol the pul-

Table 4 *Effects of acebutolol on haemodynamics*

	Before acebutolol	*During acebutolol*
Heart rate (beats/min)	83 ± 2	71 ± 1
Blood pressure (mmHg)		
Systolic	138 ± 5	120 ± 4
Diastolic	89 ± 3	82 ± 3
Cardiac output (l/min)	5·0 ± 0·2	4·5 ± 0·3
Mean pulmonary artery pressure (mmHg)	18 ± 1	18 ± 1
Mean pulmonary artery occlusive pressure (mmHg)	10 ± 1	10 ± 1

Note: Values are expressed as mean ± SE and were obtained 1 hour before acebutolol and during acebutolol treatment.

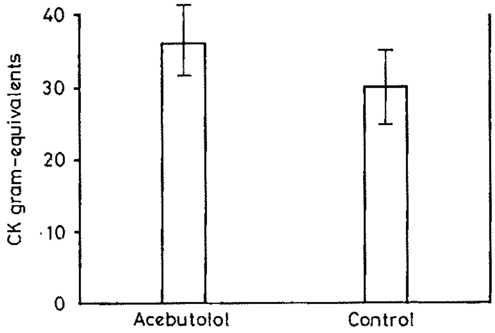

Fig. *Lack of effect of acebutolol on enzymatically estimated infarct size. The bars denote mean observed infarct size ± standard errors in treated and control groups. Mean predicted infarct sizes were equal in the two groups of patients (25 ± 4 CK gram-equivalents).*

monary artery occlusive pressure rose transiently from 10 to 20 mmHg immediately after a single dose, and returned to normal within half an hour. Neither severe bradycardia nor clinical evidence of bronchospasm was observed in any patient in the treated group. Transitory first degree heart block occurred in one patient receiving acebutolol and was the only electrophysiological complication encountered. Thus, circulatory impairment occurred in only 2 of 25 patients treated with this beta-adrenergic blocking agent and in each case it was transitory.

ENZYMATIC ESTIMATES OF INFARCT SIZE

The Figure depicts effects of acebutolol on enzymatically estimated infarct size in treated patients and controls matched for predicted infarct size. Mean observed infarct size in 25 controls was not significantly different from that in patients treated with acebutolol (30 ± 5 CK gram-equivalents compared with 37 ± 5, respectively). Observed infarct size exceeded that predicted in each group since some patients showed secondary increases in plasma CK activity presumably indicative of extension of infarction. The frequency of this occurrence was similar in the two groups (8 controls and 7 patients treated with acebutolol). Thus, administration of acebutolol beginning 6 hours after the initial plasma CK rise to patients with acute myocardial infarction without pronounced haemodynamic impairment did not appear to alter enzymatically estimated infarct size or the incidence of extension of infarction.

It should be emphasised that criteria for admission to this study were such that patients with severe haemodynamic abnormalities were excluded. In fact, all the patients in this investigation were in MIRU Class I or II. Accordingly, these results cannot be extrapolated to patients with more severe disease without appropriate further investigation.

Discussion

This study was designed to determine whether a cardioselective beta-adrenergic antagonist in dosage sufficient to reduce heart rate below 75 beats per minute would reduce the frequency or severity of ventricular arrhythmia without adversely altering haemodynamics or exacerbating injury in patients with evolving myocardial infarction. Compared with results in patients untreated but matched for incidence of arrhythmias, administration of acebutolol was associated with a significant reduction in the frequency of ventricular extrasystoles and of repetitive ventricular arrhythmias.

The beneficial effects of this agent may depend on at least two mechanisms. Acebutolol may have a direct effect on the electrophysiological stability of the myocardial cell membrane, since it ameliorates arrhythmias induced by ouabain in experimental animals (Basil *et al.*, 1974). Furthermore, acebutolol may reduce the incidence of arrhythmias by antagonising the action of circulating or locally released catecholamines (Harris *et al.*, 1971). Plasma catecholamines are raised early in the course of infarction (Karlsberg *et al.*, 1977) and may contribute to the genesis of arrhythmias by augmenting phase-4 depolarisation. In addition, catecholamines augment the release of prostaglandins (Junstad and Wennmalm, 1973) and thus may indirectly contribute to the accumulation of lysophosphoglycerides which recently have been shown to reduce reversibly the transmembrane action potential and diminish dV/dt (Corr *et al.*, 1978) and favour re-entrant arrhythmias. Moreover, the raised plasma catecholamines often accompanying myocardial infarction may augment requirements for oxygen and substrate in jeopardised tissue when oxygen delivery is limited, thereby contributing to cellular dysfunction or damage and giving rise to zones of unidirectional block facilitating re-entrant rhythms. Beta-adrenergic blockade, by attenuating these and other effects of catecholamines on the heart, may reduce the incidence of malignant disturbances of rhythm in selected patients late after infarction (Multicentre International Study, 1975). The mechanisms involved may not necessarily be the same as those accounting for observations in the present study. Nevertheless, some late episodes of malignant arrhythmia may reflect an early response to new episodes of ischaemia, and hence protective effects of beta-adrenergic blockade may resemble those seen in patients with evolving infarction in the present study.

The beneficial antiarrhythmic effects of acebutolol observed in this investigation were not accompanied by untoward effects on haemodynamics, enzymatically estimated infarct size, or the incidence of extension of infarction. Though we had expected that acebutolol might decrease infarct size by reducing myocardial oxygen consumption, at least two factors might have militated against observing this result. Firstly, reduction of myocardial damage may not be a general property of beta-adrenergic antagonists, but may be a consequence of specific molecular structure of particular agents. Nayler *et al.* (1977) have shown that L-propranolol reduces release of CK from hypoxic isolated perfused rabbit hearts, whereas comparable pharmacological doses of acebutolol do not and oxprenolol actually augments release. Though neither morphological studies nor analyses of tissue CK activity were performed to evaluate unequivocally the interpretation of results in the experimental animal study, the data suggest that propranolol might be more effective than acebutolol in preventing cell death. Recent reports of protective effects of dimethyl propranolol (Ku and Lucchesi, 1978), an agent devoid of appreciable beta-blocking activity, are compatible with this possibility.

A second factor militating against detection of protective effects on the extent of infarction of acebutolol in the present study may relate to the timing of the intervention. Protection of myocardium during evolving infarction may be possible only with interventions implemented very soon after the onset. In most studies demonstrating protection of myocardium in experimental animals (Maroko *et al.*, 1971, 1972a, b, c; Libby *et al.*, 1973; Spath, *et al.*, 1974), reduction of infarct size has been achieved with interventions initiated before or immediately after coronary artery occlusion. In contrast, clinical studies have shown no appreciable protection of myocardium with interventions initiated several hours after the onset of symptoms (Gowda *et al.*, 1975; Gillespie *et al.*, 1977). The method we used to predict infarct size entails a delay of 7 to 10 hours after the onset of symptoms before an intervention can be initiated if one wishes to preclude the influence of the intervention on projected infarct size. If beta-adrenergic antagonists are capable of protecting ischaemic myocardium in humans in a fashion analogous to protection in experimental animals, efficacy may depend on administration of the agent very early in the evolution of infarction. Thus, the fact that acebutolol did not reduce enzymatically estimated infarct size in the present study does not necessarily imply that beneficial effects would not be evident if the drug were administered earlier. On the other hand, the estimates of infarct size were undertaken to determine whether the electrophysiological effect of the drug could be obtained under typical clinical conditions without exacerbating apparent injury.

The results of this investigation indicate that acebutolol, a cardioselective beta-adrenergic antagonist, can be administered safely to selected patients with acute myocardial infarction without adversely altering haemodynamics or enzymatically estimated infarct size. The drug not only reduces heart rate, and presumably myocardial oxygen requirements, but also diminishes the frequency of ventricular extrasystoles and repetitive ventricular arrhythmias. Accordingly, it appears to be useful in enhancing cardiac electrical stability early after the onset of ischaemia in selected patients with coronary artery disease.

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Recognition and quantification of myocardial injury by means of plasma enzyme and isoenzyme activities after cardiac surgery

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SUMMARY Serial plasma enzyme determinations were carried out in 32 patients who underwent cardiac surgery with the aid of extracorporeal circulation. Plasma creatine kinase (CK), the cardiospecific isoenzyme of CK (CKMB), and alpha-hydroxybutyrate dehydrogenase (HBDH) were determined from the onset of surgery up to 100 to 120 hours after operation. From the plasma enzyme activities, the total amount of enzyme released by the injured heart into the circulation could be calculated using mathematical equations solved numerically by means of a computer. The calculated amount of CK, CKMB, and HBDH released by the heart correlated well with (1) postoperative mortality, and (2) peak activities of the respective enzymes. The calculated amount of any of the 3 enzymes released showed poor or no correlation with (1) electrocardiographic criteria of myocardial infarction, (2) duration of cardiopulmonary bypass, and (3) duration of total aortic cross-clamping.

This study shows that the extent of myocardial injury after surgery can be assessed quantitatively using the calculated amounts of enzyme released, as well as using peak plasma activities of CKMB and HBDH.

Cardiac surgery using extracorporeal circulation may be complicated by the per- and postoperative development of myocardial infarction. The diagnosis of myocardial infarction is generally based on electrocardiographic criteria of which the most specific, though not very sensitive, is the appearance of Q waves (Brewer *et al.*, 1973; Espinoza *et al.*, 1974; Rose *et al.*, 1974). However, in a number of cases the postoperative occurrence of ventricular conduction disturbances and arrhythmias such as bundle-branch block, complete heart block, or ventricular tachycardia hampers the detection of new Q waves.

Rises in the plasma enzymes aspartate aminotransferase (AST, EC 2.6.1.1), creatine kinase (CK, EC 2.7.3.2), and lactate dehydrogenase (LDH, EC 1.1.1.27) are commonly used for the diagnosis of acute myocardial infarction. This method is sensitive but non-specific, as enzymes can leak into the circulation from sources other than the heart. Examples include SGOT (AST) from the liver in the presence of congestive heart failure, LDH from erythrocytes when there is haemolysis, and CK from skeletal muscle after muscle trauma.

The introduction of isoenzyme determinations has improved the diagnostic value of enzyme tests. The cardiospecific isoenzyme of CK (CKMB) has been used successfully for the detection of acute myocardial infarction in patients in coronary care units (Konttinen and Somer, 1972; Roe *et al.* 1972; Roberts *et al.*, 1975a) and in patients undergoing aortocoronary bypass surgery (Dixon *et al.*, 1973; Oldham *et al.*, 1973; Pyle *et al.*, 1976; Warren *et al.*, 1977). Likewise the 'heart' fraction of LDH (LDH-1) has been proved to be valuable in the detection of acute myocardial infarction postoperatively (Codd *et al.*, 1975; Mohiuddin *et al.*, 1976; Codd *et al.*, 1977).

In the present study CK, CKMB, and alpha-hydroxybutyrate dehydrogenase (HBDH, an accepted method of assessing the sum of LDH-1 and LDH-2 activities) were determined in serial plasma

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Table 1 *Clinical data of 3 groups of patients:* (a) *coronary artery bypass surgery,* (b) *aortic valve replacement, and* (c) *mitral valve replacement*

	Coronary artery bypass surgery	*Aortic valve replacement*	*Mitral valve replacement*
No. of patients	15	10	7
Mean age (range) (y)	50·5 (35-62)	46·5 (22-69)	58·0 (46-68)
Sex	12 M, 3 F	8 M, 2 F	2 M, 5 F
Mean no. of grafts (range)	1·9 (1-3)		
Preoperative functional class			
(NYHA) II	1	4	0
III	13	6	5
IV	1	0	2
Cardiopulmonary bypass time (mean ± SD) (min)	118·0 ± 50·4	156·4 ± 66·8	119·6 ± 37·6
Aortic cross-clamp time (mean ± SD) (min)	34·3 ± 15·8	23·2 ± 13·1	26·1 ± 17·8
Electrocardiographic evidence of acute myocardial infarction	4	2	0
Mortality (within a week postoperatively)	2	1	0

samples for a period of 5 days in patients treated surgically for coronary artery bypass grafts or valvular replacement. From the activity curves of the plasma enzymes, the total amount per litre plasma (A) of CK, CKMB, and HBDH released by the heart into the circulation postoperatively could be calculated using a method published earlier (Witteveen *et al.*, 1975), which was slightly modified and in this study also applied to CKMB. The present study investigates the relation of the calculated A values with type of operation, postoperative mortality, electrocardiographic criteria of myocardial infarction, peak activity of plasma CK, CKMB, and HBDH, and duration of cardiopulmonary bypass and aortic cross-clamping.

Subjects and methods

PATIENTS

Thirty-two patients are included in this study. Table 1 shows the clinical data. Three groups are distinguished according to the kind of operation: aortocoronary bypass grafting (15 patients), aortic valve replacement (10 patients), and mitral valve replacement (7 patients).

METHODS

All operations were performed with standard cardiopulmonary bypass techniques. Selective coronary perfusion was used in the valvular surgery groups. Mild systemic hypothermia of 28-30°C was used in all cases, together with topical myocardial cooling with iced saline. The pulmonary bypass system was primed with lactated Ringer solution with dextrose (5%) and albumin, lowering the haematocrit from an average of 41·9 (range 50 to 33) to an average of 27·2 (range 34 to 21).

Defibrillation was effected by DC countershock of 50 J when necessary during rewarming. Duration of cardiopulmonary bypass and aortic cross-clamping is shown in Table 1.

A standard 12 lead electrocardiogram was recorded before operation and repeated at least once daily after operation. The only electrocardiographic criterion to assess myocardial infarction was the appearance of Q waves of 0·04 s duration or more (Brewer *et al.*, 1973; Espinoza *et al.*, 1974).

Ventricular conduction disturbances, such as bundle-branch block, total heart block, or severe ST-T segment changes, were considered as symptoms of acute ischaemic injury only (Codd *et al.*, 1975; Hultgren *et al.*, 1977).

ENZYME ASSAYS

Venous blood samples were taken before the first incision, immediately after termination of cardiopulmonary bypass, and subsequently every 6 hours for 100 to 120 hours. After the addition of 0·2 ml 20 per cent trisodium citrate each 10 ml sample was centrifuged at 1174 *g* for 10 minutes to remove blood cells. Thereafter the samples were stored at −20°C until they were assayed for CK, CKMB, and HBDH. CK was assayed with creatine phosphate as a substrate (Oliver, 1955) using a testkit (Baker). The isoenzymes of CK were separated by ion-exchange chromatography on DEAE-Sephadex into the 3 isoenzyme fractions: CKMM, CKMB, and CKBB (Pharmacia) (Mercer and Varat, 1975). HBDH was assayed with alphaketobutyrate as a substrate (Rosalki and Wilkinson, 1960) using a testkit (Boehringer). Enzyme activities were expressed in units (U) per litre, in which 1 U of enzyme catalyses the conversion of 1 μmol substrate per minute at 25°C.

MATHEMATICAL ANALYSIS OF ENZYME ACTIVITY DATA

By following the plasma enzyme levels sequentially one can calculate the amount of enzyme released from the infarcted or damaged area into the circulation. The quantity of enzyme released per litre of plasma during the first 24 hours after operation

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is denoted as A. The restriction to 24 hours for the calculated quantity of enzyme released is discussed below. Previously this quantity was indicated by Q (Witteveen *et al.*, 1975), but in order to avoid confusion with the electrocardiographic Q the former Q is replaced by A in the present study. A is no longer expressed in terms of grams of destroyed tissue since the quantity of enzyme released per litre of plasma is a better clinical index (Norris *et al.*, 1975).

The calculation and the mathematical model used for the calculation are described in detail elsewhere (Witteveen *et al.*, 1975). Briefly, the model is composed of two compartments, an intravascular space (volume V_i), and an extravascular space (volume V_e). Enzymes diffuse from one compartment to another with a permeability constant P and are eliminated from the plasma with a certain disappearance constant k. Using these indices, the total amount of enzyme (A) released by the infarcted area into 1 litre of plasma (U/l) can be calculated.

The period of observation was too short to obtain reliable values for the apparent disappearance rate of HBDH in individual cases, so a fixed mean value of 0·012/h was used (Witteveen *et al.*, 1975). In order to preserve comparability of results obtained for different enzymes, the same procedure was used for CK and CKMB, using the mean values of 0·046/h and 0·096/h, respectively, as determined for the total group of patients.

STATISTICAL METHODS

Statistical significance of differences between means was calculated using Student's t test for small samples. Linear regression analysis was employed to detect whether a linear correlation existed between pairs of values of two variables. Where necessary equations were used which allow for errors in both variables.

Results

Postoperative occurrence of myocardial infarction diagnosed on the basis of the development of Q waves was observed in 4 of 15 patients who received aortocoronary bypass grafts (27%) and in 2 of 17 patients with valvular replacement (12%).

Mortality during surgery and in the postoperative period of 1 week was 2 of 15 patients in the coronary bypass group (13%) and 1 of 17 patients in the valvular replacement group (6%) (Table 1). At necropsy these hearts showed definite evidence of recent myocardial infarction, confirming the electrocardiographic diagnosis made during life.

The Figure shows the A_{CK}, A_{CKMB}, and A_{HBDH} in the 3 groups of patients. The mean A values and the standard errors of the mean are listed in Table 2. The mitral valve replacement group shows significantly lower release of CK ($P < 0·05$) than the aortic valve replacement group.

Linear regression analysis was performed on the values of A_{CKMB} which is known to be cardiospecific,

Table 2 *Calculated total enzyme release per litre plasma (A, in U/l) of CK, CKMB, and HBDH in 3 groups of patients*

	Coronary artery bypass surgery (n = 15)	*Aortic valve replacement (n = 10)*	*Mitral valve replacement (n = 7)*
A_{CK}	2069 ± 500	3898 ± 1280	924 ± 130*
A_{CKMB}	92 ± 27	214 ± 93	74 ± 13
A_{HBDH}	448 ± 124	921 ± 302	299 ± 60

Indicated are mean values ± SEM.
*P < 0·05 compared with aortic valve replacement.

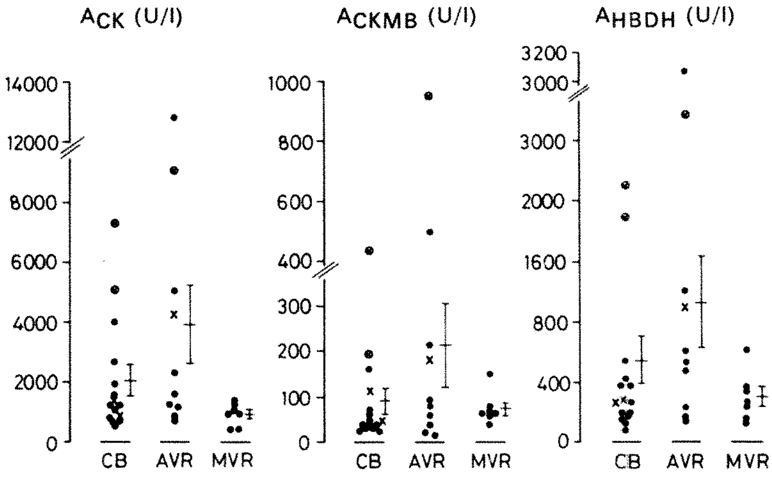

Fig. *Calculated total release (A) of CK, CKMB, and HBDH for 3 groups of patients undergoing open-heart surgery: aortocoronary bypass grafting (CB, n = 15), aortic valve replacement (AVR, n = 10), and mitral valve replacement (MVR, n = 7). Indications are given of patients who did not survive the postoperative period of 1 week (o) and of patients who developed electrocardiographic signs of acute myocardial infarction postoperatively (Q waves) (x). Bars represent mean values ± SEM.*

Table 3 *Correlation coefficients obtained from linear regression analysis on data of calculated total enzyme release per litre plasma (A) of CK, CKMB, and HBDH in patients after cardiac surgery*

	All patients (n = 32)	*Coronary artery bypass surgery (n = 15)*	*Aortic valve replacement (n = 10)*	*Mitral valve replacement (n = 7)*
A_{CKMB} vs. A_{CK}	0·846	0·911	0·818	0·736
A_{CKMB} vs. A_{HBDH}	0·840	0·832	0·827	0·867
A_{HBDH} vs. A_{CK}	0·959	0·872	0·989	0·775

together with those of A_{CK} and A_{HBDH}, to investigate whether CK and HBDH released postoperatively also originate from the myocardium. Table 3 shows the correlation coefficients. In the mitral valve replacement group a relatively low correlation coefficient (0·736) is found, partly because of the low A values in this group of patients (see Figure) and the small number of patients ($n = 7$). Nevertheless, the data in Table 3 seem to indicate a close overall correlation between the A values of the 3 enzymes, showing that the greater part of CK and HBDH released into the circulation in the postoperative period originated from the heart muscle tissue. The whole range of A values has been divided arbitrarily into 3 parts in order to interpret A values in terms of myocardial damage (Table 4). The lowest range of A values ($A_{CK} < 1500$ U/l; $A_{CKMB} < 75$ U/l; and $A_{HBDH} < 400$ U/l) represents slight myocardial damage, present in 60 to 73 per cent of the coronary bypass patients, in 30 to 40 per cent of the patients with aortic valve replacement, and in 71 to 100 per cent of the patients with mitral valve replacement, these percentages varying with the enzyme used. Patients in this low range of A values all survived operation and the postoperative period of 1 week. However, a few patients in the coronary bypass group with low A values had new Q waves postoperatively. Since new Q waves are specific indicators of acute myocardial infarction, infarctions may have occurred, which were small in size as concluded from the low values of enzyme release, and had no harmful effect on the postoperative recovery of the patients.

The intermediate range of A values (A_{CK}: 1500-3000 U/l; A_{CKMB}: 75 to 150 U/l; and A_{HBDH}: 400 to 800 U/l) represents moderate myocardial damage, present in 7 to 20 per cent of the coronary bypass patients, in 20 to 30 per cent of the patients with aortic valve replacement, and in 0 to 29 per cent of the patients with mitral valve replacement, these percentages varying with the enzyme used. Patients in this intermediate range of A values all survived. Only 1 patient in the coronary bypass group with an intermediate A_{CKMB} value showed new Q waves on the electrocardiogram, probably indicating the postoperative development of non-fatal myocardial infarction.

The highest range of A values ($A_{CK} > 3000$ U/l; $A_{CKMB} > 150$ U/l; and $A_{HBDH} > 800$ U/l) represents extensive myocardial damage, present in 13 to 20 per cent of the coronary bypass patients, the percentage varying with the enzyme used, and in 40 per cent of the patients with aortic valve replacement. None of the patients in the mitral valve replacement group had A values in the highest range.

Postoperative death was associated with the high A values: in the coronary bypass group 67 to 100 per cent of the patients with high A values died, the percentage varying with the enzyme used, and in the aortic valve replacement group 25 per cent of the patients with high A values died. The hearts of these patients all showed extensive recent myocardial infarctions at necropsy. Application of the

Table 4 *Comparison of 3 ranges of values of A_{CK}, A_{CKMB}, and A_{HBDH} with number of patients, postoperative development of new Q waves in electrocardiogram, and postoperative mortality in 3 surgery groups*

	Coronary bypass surgery (n = 15)			*Aortic valve replacement (n = 10)*			*Mitral valve replacement (n = 7)*			*Extent of myocardial damage based on the value of A*
	No. of cases	*Q waves*	*Postop. death*	*No. of cases*	*Q waves*	*Postop. death*	*No. of cases*	*Q waves*	*Postop. death*	
A_{CK} (U/l)										
< 1500	9	2	0	4	0	0	7	0	0	Slight
1500 – 3000	3	0	0	2	0	0	0	0	0	Moderate
> 3000	3	2	2	4	2	1	0	0	0	Extensive
A_{CKMB} (U/l)										
< 75	11	1	0	4	0	0	5	0	0	Slight
75 – 150	1	1	0	2	0	0	2	0	0	Moderate
> 150	3	2	2	4	2	1	0	0	0	Extensive
A_{HBDH} (U/l)										
< 400	11	2	0	3	0	0	6	0	0	Slight
400 – 800	2	0	0	3	0	0	1	0	0	Moderate
> 800	2	2	2	4	2	1	0	0	0	Extensive

χ^2 test on the distribution of non-survivors among the 3 ranges of A values showed a highly significant ($P < 0{\cdot}01$) association of mortality with the highest range of A values of any of the 3 enzymes. Of the patients in the coronary bypass group having high A values, 67 to 100 per cent showed Q waves postoperatively, dependent on the enzyme used. In the mitral valve replacement group this incidence was 50 per cent. Since Q waves can be found through the whole range of A values and mortality was always associated with the highest range of A values, it is believed that A values are more relevant than the presence of Q waves in the electrocardiogram to assess the extent of myocardial damage after open-heart surgery. When the ranges (low, intermediate, and high) in A_{CK}, A_{CKMB}, and A_{HBDH} were compared for each patient, it was found that in 75 per cent of the cases the 3 ranges were identical (for example, A_{CK}: low, A_{CKMB}: low, and A_{HBDH}: low). In 25 per cent of the cases the ranges for 2 enzymes were identical, the range for the third enzyme having shifted to a neighbouring category (for example, A_{CK}: low, A_{CKMB}: low, and A_{HBDH}: intermediate).

Investigations were carried out to see if the maximum plasma level (peak activity) was an equally reliable index of myocardial injury as the calculated A value. Therefore we correlated the peak activities in plasma of CK, CKMB, and HBDH corrected for the respective preoperative activities with A_{CK}, A_{CKMB} and A_{HBDH}, respectively, in the 3 groups of patients. Table 5 shows the correlation coefficients, which show that for diagnostic purposes one may rely on peak plasma enzyme activities corrected for respective preoperative activities in addition to A values. The former are obtained more easily than the latter.

The time lapse between the start of the operation and the moment the enzyme reaches its maximal activity in plasma is referred to as peak arrival time of that enzyme. Table 6 shows the peak arrival times of CK, CKMB, and HBDH in the 3 groups of patients. It appears that the peak arrival time of CKMB is significantly shorter in the mitral valve replacement group than in the coronary bypass group ($P < 0{\cdot}01$) and the aortic valve replacement group ($P < 0{\cdot}01$). The A values of CK, CKMB, and HBDH did not show any significant correlation with aortic cross-clamp time in either of the 3 groups of patients. The same is true for the cardiopulmonary bypass time, except for A_{CKMB} ($r = 0{\cdot}94$) and A_{HBDH} ($r = 0{\cdot}80$) in the mitral valve replacement group.

Table 5 *Correlation coefficients obtained from linear regression analysis on data of calculated total enzyme release per litre plasma (A) and peak* enzyme activity in plasma corrected for preoperative activity, both expressed in U/l, in 3 groups of patients*

	All patients (*n* = *32*)	*Coronary bypass surgery* (*n* = *15*)	*Aortic valve replacement* (*n* = *10*)	*Mitral valve replacement* (*n* = *7*)
CK	0·989	0·986	0·996	0·815
CKMB	0·962	0·974	0·957	0·982
HBDH	0·991	0·993	0·995	0·524

*Highest enzyme activity in plasma in the first 24 hours after onset of surgery.

Table 6 *Peak arrival times, expressed in hours, of CK, CKMB, and HBDH in plasma of 3 groups of patients*

	Coronary artery bypass surgery (*n* = *15*)	*Aortic valve replacement* (*n* = *10*)	*Mitral valve replacement* (*n* = *7*)
CK	30·7 ± 3·0	29·2 ± 4·8	20·2 ± 4·0
CKMB	12·9 ± 1·4	12·9 ± 2·0	6·5 ± 1·1
HBDH	23·2 ± 3·0	21·1 ± 2·2	22·8 ± 6·4

Indicated are mean values ± SEM.

Discussion

Acute myocardial infarction is a frequent complication of cardiac surgery, especially when the cardiopulmonary bypass procedure is used. Postoperative electrocardiographic evidence of acute myocardial infarction occurs in 6 to 30 per cent of the patients undergoing aorto-coronary bypass grafting (Hultgren *et al.*, 1971; Bolooki *et al.*, 1972; Alderman *et al.*, 1973; Bolooki *et al.*, 1973; Brewer *et al.*, 1973; Oldham *et al.*, 1973; Espinoza *et al.*, 1974; Ghani *et al.*, 1974; Rose *et al.*, 1974; Codd *et al.*, 1975; Mohiuddin *et al.*, 1976; Codd *et al.*, 1977; Hultgren *et al.*, 1977; Klein *et al.*, 1977; Warren *et al.*, 1977). In patients undergoing valvular replacement 0 to 14 per cent developed electrocardiographic abnormalities characteristic of acute myocardial infarction (Ghani *et al.*, 1974; Rose *et al.*, 1974; Hultgren *et al.*, 1977; Klein *et al.*, 1977). Mortality during aortocoronary bypass grafting and in the postoperative period is reported to be 1·1 to 10·7 per cent (Bolooki *et al.*, 1972; Brewer *et al.*, 1973; Dixon *et al.*, 1973; Oldham *et al.*, 1973; Espinoza *et al.*, 1974; Ghani *et al.*, 1974; Rose *et al.*, 1974; Mohiuddin *et al.*, 1976; Codd *et al.*, 1977; Hultgren *et al.*, 1977; Warren *et al.*, 1977). The mortality in a group of patients who were surgically treated for valvular replacement is 3·9 per cent (Ghani *et al.*, 1974).

The development of new Q waves in the electrocardiogram can be considered a specific, but rather insensitive criterion for acute myocardial infarction (Espinoza *et al.*, 1974; Warren *et al.*, 1977). Other criteria sensitive for myocardial injury, either ischaemia or infarction, that can be used are rises in plasma enzymes (Shirey *et al.*, 1970; Hultgren *et al.*, 1971; Alderman *et al.*, 1973; Bolooki *et al.*, 1973; Ghani *et al.*, 1974; Neutze *et al.*, 1974; Rose *et al.*, 1974; Hultgren *et al.*, 1977). More recently, rises in isoenzymes of CK (CKMB) and LDH (LDH-1) in plasma are used for the diagnosis of myocardial injury (Dixon *et al.*, 1973; Oldham *et al.*, 1973; Codd *et al.*, 1975; Mohiuddin *et al.*, 1976; Pyle *et al.*, 1976; Codd *et al.*, 1977; Warren *et al.*, 1977). Both CKMB and LDH-1 are raised in myocardial infarction, or more generally in myocardial injury. In patients with acute myocardial infarction admitted to the coronary care unit plasma enzymes and isoenzymes have not only provided the clinician with a means to diagnose acute myocardial infarction, but also with a method to assess the size of the infarct (Sobel *et al.*, 1972; Witteveen *et al.*, 1975).

Infarct sizes of patients having acute myocardial infarction in the coronary care unit showed good correlation with prognosis (Sobel *et al.*, 1972; Norris *et al.*, 1975), functional class according to the NYHA criteria (Sobel *et al.*, 1972), the presence of pulmonary venous congestion or pulmonary oedema (Norris *et al.*, 1975), left ventricular haemodynamics (Mathey *et al.*, 1974; Rogers *et al.*, 1977), and incidence of ventricular arrhythmias (Roberts *et al.*, 1975b).

In this study we investigated patients who underwent cardiac surgery with the aid of extracorporeal circulation. The calculated amounts of CK, CKMB, and HBDH released postoperatively by the heart into the circulation showed good correlations with each other (Table 3), with mortality (Table 4), and with peak plasma activities of CK, CKMB, and HBDH, respectively (Table 5).

The relation between postoperative plasma enzyme or isoenzyme activity and duration of cardiopulmonary bypass as well as total aortic cross-clamping time was established earlier in patients receiving aortocoronary bypass grafts and valvular replacement (Oldham *et al.*, 1973; Ghani *et al.*, 1974; Neutze *et al.*, 1974; Codd *et al.*, 1975; Pyle *et al.*, 1976). However, except for the patients undergoing mitral valve surgery, no significant correlation was found between cardiopulmonary bypass time and A values. No correlation was observed between aortic cross-clamping time and A values in either group of patients. The A values for CK in patients of the aortic valve replacement group were significantly higher ($P < 0{\cdot}05$) than those in patients of the mitral valve replacement group. Associated with this difference is a longer cardiopulmonary bypass period in the aortic valve replacement group (156·4 min) compared with that in the mitral valve replacement group (119·6 min), though this difference was not significant. Peak arrival time of CKMB was significantly longer in the patients of the aortic valve replacement group (12·9 hour) than in the patients of the mitral valve replacement group (6·5 hour) ($P < 0{\cdot}01$) (Table 6). An explanation for these differences between the valvular replacement groups is probably given by the hypertrophied state of the hearts in the aortic valve replacement group. In these hypertrophied hearts, whether concentric or dilated, the selective perfusion of the coronary arteries during the period of cardiopulmonary bypass may be inadequate in perfusing the subendocardial layers of the heart. As cardiopulmonary bypass lasts for an average of 156 minutes, this period may be long enough to promote the development of extensive subendocardial ischaemia, leading to a considerable amount of enzyme released before and directly after disconnection of extracorporeal circulation.

Table 7 *Peak arrival times, expressed in hours, of CK, CKMB, and HBDH in patients who underwent coronary artery bypass surgery and in patients with acute myocardial infarction admitted to coronary care unit (CCU)*

	Surgery	*Acute myocardial infarction in CCU*	*P*
CK	30·7 ± 3·0 (15)	22·9 ± 1·7 (10) (Witteveen *et al.*, 1975)	< 0·05
CKMB	12·9 ± 1·4 (15)	18·0 ± 0·5 (31) (Fiolet *et al.*, 1977)	<0·01
HBDH	23·2 ± 3·0 (15)	39·1 ± 2·2 (10) (Witteveen *et al.*, 1975)	<0·01

Indicated are mean values ± SEM; number of patients is indicated in parentheses. P: surgery vs. acute myocardial infarction.

As shown in Table 7, the peak arrival times of CKMB and HBDH are earlier after surgery than after acute myocardial infarction, while for CK the reverse is true. The same phenomenon was apparent from inspection of the release curves, that is the time derivative of the quantity A. While the release of enzyme after acute myocardial infarction usually lasts for at least 48 hours (Witteveen *et al.*, 1975), the release of CKMB and HBDH was completed within 24 hours after operation in the majority of cases, while the release of CK continued for more than 60 hours. This observation strongly suggests a prolonged leakage of CK from damaged skeletal muscle after surgery. The earlier appearance of cardiac enzymes after surgery, compared with acute myocardial infarction, has been described as a washout phenomenon after reflow of ischaemic myocardium (Jarmakani *et al.*, 1976; Maroko and

Vatner, 1977). As a consequence of these findings the calculation of A was restricted to the first 24 hours after operation in order to ensure that myocardial enzyme release was studied. As skeletal muscle contributes late to the CK activity in plasma, the CK release during the first 24 hours will be mainly from the heart; this explains the high correlations of A_{CK} with $A_{CK\,MB}$ and A_{HBDH} (Table 3).

Of the 3 enzymes used in this study CKMB and HBDH are most appropriate for the calculation of the total amount of enzyme released by the injured heart into the circulation. As the chromatographic separation of CKMB is a time-consuming procedure, especially if many plasma samples have to be assayed, the use of HBDH is preferred to that of CKMB. Only when moderate or severe haemolysis is present in the plasma samples, is CKMB the enzyme of choice for recognition and quantification of myocardial injury after cardiac surgery.

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Estimation of myocardial infarct size in man using 99^m Tc polyphosphate

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SUMMARY We have critically evaluated the use of 99^m Tc polyphosphate to estimate myocardial infarct size. Optimum conditions were first defined with respect to infarct edge definition, and relative activity over infarct and bone and in the blood pool. The scintigrams of 53 patients with acute transmural myocardial infarction were recorded under these defined constant conditions and analysed in various ways. Visual grading of infarct area or intensity correlated poorly with other indices of infarct severity. Computer-assisted measurements of above-background infarct uptake area or of total infarct activity correlated well with clinical, electrocardiographic, and enzymatic measurements of infarct severity.

The observation that 99^m technetium stannous pyrophosphate accumulates in a developing myocardial infarct has led to its use with the scintillation camera in clinical practice (Bonte *et al.*, 1975). Animal work has shown that there is good correlation between infarct uptake on surface scintigrams and actual infarct size (Botvinick *et al.*, 1975; Stokely *et al.*, 1976). There has, however, been little attempt to correlate scintigraphic estimates of infarct size with other evidence of infarct severity in man (Willerson *et al.*, 1977). 99^m Tc polyphosphate has also been used for infarct imaging (McLaughlin *et al.*, 1975) but less extensively. It has the potential advantage of a higher infarct/bone uptake ratio as indicated from animal experiments (Bonte *et al.*, 1974).

We have therefore critically evaluated the use of 99^m Tc polyphosphate to estimate infarct size. In particular we examined the time course of relative infarct, bone, and blood pool activity, and measured the sharpness of infarct edge definition, with a view to obtaining optimal conditions for this technique. 99^m Tc polyphosphate scintigrams were then obtained under these defined and precisely constant conditions in 53 patients with acute transmural infarction. The infarct image was measured in various ways and correlated with clinical, electrocardiographic, and biochemical indices of infarct severity. Visual estimates correlated poorly but computer-assisted measurements of infarct area correlated well with these other criteria of infarct severity.

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Methods

Seventy-one patients were studied: 57 men and 14 women aged between 35 and 72 years.

Group 1 consisted of 53 patients who fulfilled all 3 criteria for acute myocardial infarction: (i) typical cardiac pain lasting 1 hour or longer and starting within 8 hours of admission: (ii) 12 lead surface electrocardiographic abnormalities of 'very probable' acute myocardial infarct (WHO criteria), and (iii) serum total CK level >220 IU/l (normal <110 IU/l) in the initial or the next two daily measurements done routinely in every patient.

Group 2 consisted of 18 patients who had acute coronary insufficiency fulfilling criterion (i) but not (ii) or (iii), and showing ischaemic T wave changes or transient ST segment shift (>2 mm) on the electrocardiogram.

CLINICAL CLASSIFICATION (GROUP 1)

Class 1: no clinical or radiological evidence of pulmonary oedema or circulatory disturbance. *Class 2:* mild pulmonary oedema, with basal crepitations, a diastolic filling sound, and radiological upper-zone pulmonary venous dilatation. *Class 3:* severe pulmonary oedema with or without cardiogenic shock (systolic BP<90 mmHg, peripheral coldness, sweating, urine volume <20 ml/h).

ELECTROCARDIOGRAPHIC CLASSIFICATION (GROUP 1)

Anterior infarct
Class 1: localised, with pathological Q waves in only V2 and/or V3. *Class 2:* extensive, with pathological Q waves in 4 or more of chest leads. *Class 3:* extensive, with bifascicular block in addition.

Inferior infarct
Class 1: localised, with pathological Q waves only in leads II and/or III and/or aVF. *Class 2:* extensive, with lateral and/or posterior extension, that is with pathological Q waves also in the lateral chest leads and/or increase in R wave voltage in chest leads V1-3.

CK CLASSIFICATION (GROUP 1)

The serum total CK was measured one hour after admission and at 9 am on each of the first 3 days (but excluding the first day when admission was between 3 and 8 am). The sum of the first 3 measurements of serum total CK levels was used as a crude enzymatic index of infarct size: *class 1:* <1000 IU/l; *class 2:* 1000-2000 IU/l; *class 3:* 2000-2500 IU/l; *class 4:* >2500 IU/l.

TECHNIQUE OF RECORDING SCINTIGRAMS

Scintigrams were recorded ¾ to 1 hour and 2 to 2½ hours after intravenous injection of 10 mCi 99^{m} Tc polyphosphate. Scintigrams were recorded on day 1 and on day 2 or 3, each day representing a 24-hour period with reference to the onset of chest pain. A General Electric Radicamera II was used with a 20 per cent window centred upon 140 Kev. Each scintigram consisted of a total of 300 000 counts and was stored in frame mode as a 64 × 64 matrix on high density disc (BASF systems HD8). A Nuclear Data (ND812) digital computer was used for subsequent data analysis with constant display size.

Records were obtained with the patient in the supine projection, or in patients with severe pulmonary oedema in the 45° head-up tilt position. In each case scintigrams were recorded in the anteroposterior (AP), 45° left anterior oblique (LAO), and left lateral (LL) projections (with the patient's arms above the head in the last two of these projections).

CLEARANCE OF 99^{M} TC POLYPHOSPHATE

Serial blood samples were taken from 10 minutes to 4 hours after the isotope injection. Each sample was immediately divided into two, one being stored as whole blood, and the other immediately centrifuged and stored as plasma. Samples were subsequently counted at the same time in a well scintillation detector.

INFARCT/BONE RATIO

Scintigrams were recorded in the identical left lateral projection in each patient. Measurements were made in two representative rectangular areas

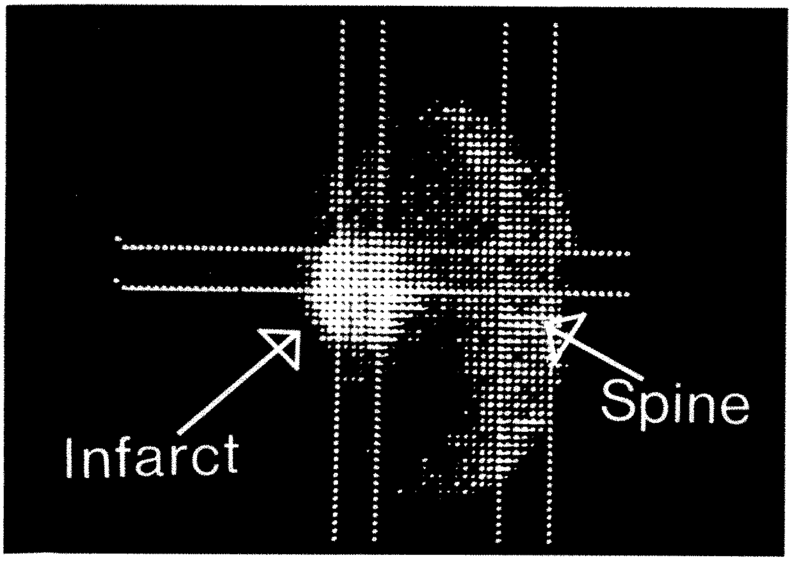

Fig. 1 *Horizontal and vertical markers enclosing rectangular areas of interest over the infarct image and spine image for measurement of infarct/bone uptake ratio.*

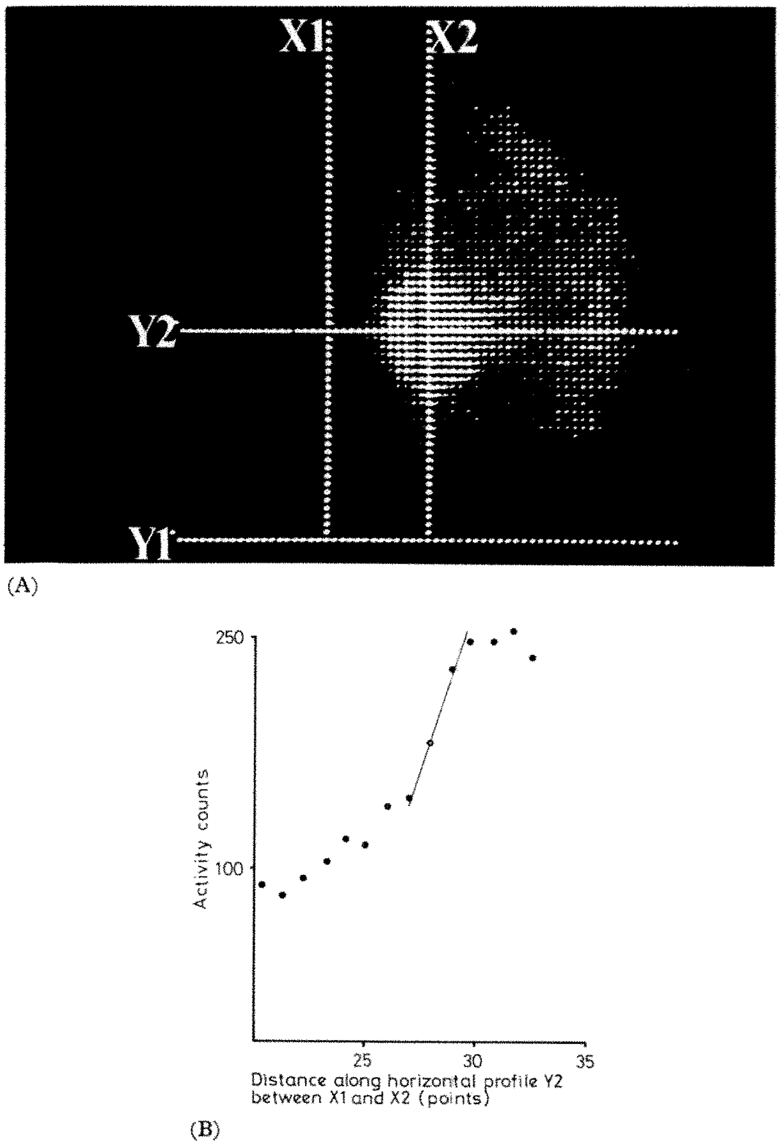
X1
X2
Y2
Y1
(A)
250
100
Activity counts
25
30
35
Distance along horizontal profile Y2 between X1 and X2 (points)
(B)

Fig. 2 *Definition of infarct edge. (A) ^{99m} Tc polyphosphate scintigram (LAO projection). Horizontal marker (Y2) crosses the infarct edge in its traverse between vertical markers, X1 and X2. (B) Profile of increasing activity across infarct edge. Computer read-out of counts over successive points along Y2 between X1 and X2 (Fig. 2A). Line is best fit through 4 adjacent points of steepest slope. Its slope represents sharpness of definition of infarct edge.*

within the region of the 'infarct' uptake and in the two corresponding areas at the same horizontal level over the spine (Fig. 1). The average count density over the infarct was compared with that over the spine to give the infarct/bone ratio.

INFARCT EDGE DEFINITION

Scintigrams were recorded as above. Count density was plotted along a profile selected as passing through the infarct edge (in an intercostal space). An index of the sharpness of definition of the infarct edge was obtained from steepness (estimated peak slope) of the change in counts across the edge (Fig. 2A and B). In each scintigram the average peak slope derived from two parallel profiles was calculated. In each patient it was clearly critically important that corresponding scintigrams recorded at different times represented identical profiles as nearly as possible. In order to achieve this the camera position and angle were maintained constant relative to the floor. The patient was positioned to lie supine on a hard table of constant height from the floor and in an identical place on the table with respect to the position of the head and feet. A protruding rigid arm from the camera was related to a constant anatomical landmark on each patient further to ensure precisely constant positioning.

Profiles were horizontal, through lung, heart, infarct, and spine, and as they were in the LAO projection the anterior portion of these profiles avoided rib activity. Activity along the profile fell to a low plateau anteriorly, presumably over normal heart and lungs, and the level of this plateau was taken to represent 'background activity'.

ELECTROCARDIOGRAPH GATING

A synchronising unit was used, triggered by the leading edge of the R wave—derived 'SYNC' output of a Hewlett Packard 7807B patient electrocardiograph monitor. The 'dwell' period was fed to the 'GATE' input of the gamma camera analogue computer module which, in the absence of the signal, was held off. Thus data were acquired only during the 'dwell' period. To facilitate setting up, a duplicate of the 'dwell' signal was applied to the second channel of the patient monitor oscilloscope. Scintigrams were recorded consisting of 300 000 counts with and without electrocardiograph gating. Edge analysis was performed as described above.

SCINTIGRAPHIC ASSESSMENT OF INFARCT SIZE

Scintigrams recorded between 2 and 2½ hours after isotope injection on day 2 or 3 were used. Assessment was made (a) by subjective grading of one projection, (b) by subjective grading of three projections, and (c) by computer-assisted measurement of above-background counts within the subjectively delineated area of the infarct in one projection.

Assessment was blind, without knowledge of related clinical, electrocardiograph, or enzyme data. Infarcts were subjectively graded from 1 to 3 according to increasing area and from 1 to 3 according to increasing density of isotope uptake, the sum of the two giving an index of infarct size. The index was assessed in each case (a) from the single LAO projection, and (b) from the sum of the indices in the AP, LAO, and LL projections. (c) Three different horizontal profiles were plotted to give 'background activity' (Fig. 3) which was subtracted from total activity over the infarct to give a clearer image of specific 'infarct activity'. By projecting the resultant specific 'infarct activity', the area of the infarct was more easily outlined with a light pen, extrapolating across overlying ribs between intercostal spaces. The total 'infarct activity' within this area was analysed with the aid of the computer to give the number of points (computed area) showing 'infarct activity' and the total number of counts (total activity) within the delineated infarct area, from which was also derived the average number of counts/point (computer average uptake density). Rib uptake will, therefore, contribute to total infarct activity, but it will not influence measurement of 'infarct area', nor should it seriously affect estimates of relative 'intensity', 'total computed infarct activity', or 'average uptake density' compared at different times and in different patients.

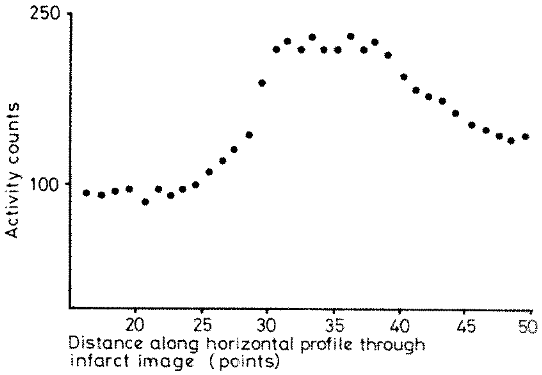

Fig. 3 *Profile of counts along a horizontal marker through infarct for estimation of background activity immediately surrounding infarct. Line is drawn through ventral background only, because dorsal background is influenced by activity over spine. Average of 3 different profiles is used in each case.*

STATISTICAL ANALYSIS

This was by Student's t test for paired data except as otherwise indicated. Results are expressed as mean ± standard deviation, and considered significantly different when $P < 0{\cdot}05$.

Results

CLEARANCE OF 99^{M} TC POLYPHOSPHATE

Fig. 4 shows the clearance curves which are

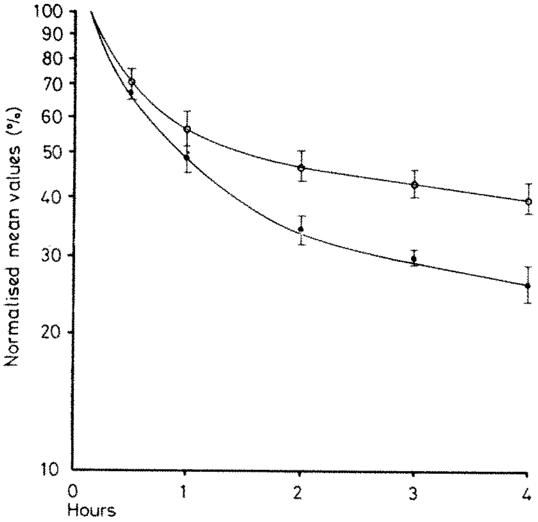

Fig. 4 *Clearance of 99^{m} Tc polyphosphate from whole blood and plasma. Samples were taken at times indicated, and measured at the same time later, so that the curves represent biological clearance and not radioactive decay. (Mean ± SD, n = 5).* ○ = *whole blood;* ● = *plasma.*

biexponential with half-times in whole blood of 18·5 minutes and 7 hours 45 minutes, and in plasma of 16·5 minutes and 5 hours.

INFARCT/BONE RATIO

Infarct/bone ratio was significantly higher (P < 0·02) 1 hour after isotope injection (0·960 ± 0·139, n = 20) than 2½ hours after injection (0·848 ± 0·132) in scintigrams recorded on day 2 or 3.

Infarct/bone ratio 2½ hours after injection was significantly higher (P < 0·001) on day 2 (n = 7) or day 3 (n = 3) (1·101 ± 0·292, n = 10) than on day 1 (0·898 ± 0·111).

INFARCT EDGE DEFINITION

The infarct edge was significantly more sharply defined 2 to 2½ hours after isotope injection than 1 hour after injection. The mean peak slope of difference in count density along profiles through the infarct edge was 16·162 ± 11·568 counts/interval between adjacent points at 2 to 2½ hours compared with 10·219 ± 4·12 counts/interval at 1 hour, n = 24, P < 0·001.

The infarct edge was significantly more sharply defined on day 2 (n = 17) or 3 (n = 7) than on day 1. On day 2 or 3 the slope was 22·915 ± 15·271, compared with 11·0 ± 7·139 on day 1, n = 10, P < 0·001.

Electrocardiograph gating did not significantly improve the definition of the infarct edge. In scintigrams recorded 2 hours after isotope injection on the 2nd day in hospital, the slope across the infarct edge was 15·729 ± 6·641 counts/interval without electrocardiograph gating, and 18·114 ± 8·425 with gating, n = 7, P > 0·05.

SCINTIGRAPHIC FINDINGS RELATED TO CLINICAL DIAGNOSIS

Of the 53 patients with myocardial infarction (group 1), 52 had positive scintigrams and 1 was equivocal. This was in a patient whose scintigram was recorded only at 18 hours after the onset of chest pain and who had a localised (class 1) inferior infarct.

Of 10 patients with scintigrams recorded within the first 12 hours, 8 had positive scintigrams and 2 were negative. The patients with negative scintigrams at this time (one with an anterior, class 1, infarct, measured at 6 hours, the other with an inferior, class 1, infarct, measured at 5 hours) both showed positive scintigrams on day 3. Of 24 patients where scintigrams were recorded during the first 24 hours after the onset of chest pain, 20 had positive scintigrams, 2 were equivocal, and 2 (detailed above) were negative. Of the 2 patients with equivocal scintigrams, one is detailed above; the other was recorded at 14 hours in a patient with a class 3 anterior infarct, and a repeat scintigram at 5 days was positive. Of 30 patients studied on day 2 or 3, all showed positive scintigrams. Of 9 patients studied on days 4 and 5, 8 had positive scintigrams, and 1 (studied on day 4, class 1, inferior infarct) was equivocal.

Of the 18 patients with acute coronary insufficiency (group 2), 13 had positive scintigrams, 2 were equivocal, and 3 were negative. Of the 13 positive scintigrams, 4 were recorded on day 1, 5 on day 2, 3 on day 3, and 1 on day 5. Three patients with positive scintigrams experienced continuing angina despite medical treatment and 3 patients developed acute myocardial infarction (fulfilling the diagnostic criteria described above), 2 during the same admission (day 5 and day 6) and 1 three months later. In the other 10 patients with positive scintigrams, continued serial electrocardiograph monitor recordings and measurements of serum CK showed no changes of myocardial infarction. All 3 patients with negative scintigrams became asymptomatic on treatment with oxprenolol.

CORRELATION OF INDEXED SEVERITY OF INFARCT FROM SCINTIGRAMS WITH CLINICAL, ELECTROCARDIOGRAPHIC, AND CK CLASSIFICATION

Table 1 shows that from the LAO projection alone, the indexed *area* of uptake (see Methods, scinti-

Table 1 *Visual analysis: scintigraphic index of severity of infarct (LAO projection)*

Clinical class		*No.*	*Area log index*	*Intensity log index*	*Area and intensity log index*
	1	17	0·272 ± 0·133	0·230 ± 0·213	0·565 ± 0·136
	2	12	0·349 ± 0·082*	0·307 ± 0·121	0·620 ± 0·100
	3	10	0·389 ± 0·093*	0·371 ± 0·091*	0·686 ± 0·066*†
Electrocardiogram class					
Anterior	1	5	0·301 ± 0·100	0·366 ± 0·167	0·635 ± 0·098
	2	10	0·389 ± 0·093	0·354 ± 0·085	0·676 ± 0·071
	3	5	0·366 ± 0·079	0·336 ± 0·079	0·612 ± 0·107†
Inferior	1	14	0·274 ± 0·165	0·219 ± 0·180	0·560 ± 0·136
	2	5	0·371 ± 0·096*	0·251 ± 0·240	0·626 ± 0·140
CK class					
	1	15	0·255 ± 0·134	0·263 ± 0·199	0·566 ± 0·116
	2	12	0·306 ± 0·115	0·287 ± 0·185	0·603 ± 0·132
	3	9	0·360 ± 0·088*	0·340 ± 0·078*	0·654 ± 0·066*†
	4	6	0·389 ± 0·096*	0·389 ± 0·096*	0·672 ± 0·116*

For definition of clinical, electrocardiogram, and CK classes see Methods.

Footnote: Data are analysed by logarithmic transformation to compare geometric means, and are given as mean ± SD of log 10 index.
*Indicates P < 0·05 compared with respective class 1.
†Indicates P < 0·05 compared with preceding class, where this is not class 1.

graphic assessment of infarct size, method (a)) was significantly greater in clinical class 2 or 3 than class 1, significantly greater in electrocardiogram class 2 than class 1 inferior infarcts, but not significantly different in different electrocardiogram classes of anterior infarcts or different CK classes. The indexed *intensity* of uptake showed no significant differences between adjacent clinical electrocardiogram or CK classes but distinguished between clinical class 1 and 2 and also between CK classes 3 or 4 compared with 1. The *combined* index of area and intensity was greater in clinical class 3 than 1 or 2, and significantly greater in CK classes 3 or 4 compared with 1 or to 2.

Table 2 shows that, from the combination of AP, LAO, and LL projections, the indexed *area* of uptake was significantly greater in clinical class 3 than classes 2 or 1 and in clinical class 2 than class 1. The *area* was greater in electrocardiogram class 2 than class 1 inferior infarcts, though not significantly different in the different electrocardiogram classes of anterior infarct. It was greater in CK class 4 than in classes 3, 2, or 1. The indexed *intensity* of uptake was greater in clinical class 3 than 2. It did not correlate positively with electrocardiogram classes of severity or between adjacent CK classes although the index was significantly greater in CK classes 3 and 4 compared with 1. The *combined* index of area and intensity was greater in class 3 than classes 2 or 1. It was greater in extensive than in localised inferior infarcts, but did not distinguish between anterior infarcts of differing severity. It was greater in CK class 4 than classes 3, 2, or 1, and in CK class 3 than class 1.

Table 2 *Visual analysis: scintigraphic index of severity of infarct (combined AP, LAO, and LL projections)*

Clinical class		*No.*	*Area log index*	*Intensity log index*	*Area and intensity log index*
	1	17	0·686 ± 0·177	0·716 ± 0·135	1·009 ± 0·133
	2	12	0·774 ± 0·130*	0·667 ± 0·125	1·028 ± 0·114
	3	10	0·876 ± 0·068*†	0·791 ± 0·146†	1·147 ± 0·042*†
Electrocardiogram class					
Anterior	1	5	0·715 ± 0·143	0·777 ± 0·131	1·049 ± 0·133
	2	10	0·848 ± 0·091	0·792 ± 0·117	1·129 ± 0·069
	3	5	0·846 ± 0·111	0·705 ± 0·180†	1·088 ± 0·078
Inferior	1	14	0·658 ± 0·172	0·703 ± 0·149	0·989 ± 0·136
	2	5	0·769 ± 0·098*	0·721 ± 0·177	1·032 ± 0·134*
CK class					
	1	15	0·701 ± 0·164	0·682 ± 0·165	0·992 ± 0·137
	2	12	0·757 ± 0·150	0·726 ± 0·162	1·048 ± 0·138
	3	9	0·768 ± 0·099	0·759 ± 0·101*	1·060 ± 0·083*
	4	6	0·888 ± 0·076*†	0·817 ± 0·141*	1·156 ± 0·080*†

For definition of clinical, electrocardiogram, and CK classes see Methods.

Footnote: Data are analysed by logarithmic transformation to compare geometric means, and are given as mean ± SD of log 10 index.
*Indicates P < 0·05 compared with respective class 1.
†Indicates P < 0·05 compared with respective preceding class, where this is not class 1.

Table 3 *Quantitative analysis: left anterior oblique projection*

Clinical class		*No.*	*Area log no. of points*	*Total activity* *Total no. of counts*	*Average uptake density* *Log counts/point*
	1	17	1·639 ± 0·291	3·574 ± 0·368	1·935 ± 0·281
	2	12	2·032 ± 0·296*	3·932 ± 0·206*	1·900 ± 0·155
	3	10	2·386 ± 0·163*†	4·228 ± 0·149*†	1·843 ± 0·148
Electrocardiogram class					
Anterior	1	5	1·705 ± 0·345	3·726 ± 0·281	2·021 ± 0·220
	2	10	2·215 ± 0·135*	4·077 ± 0·120*	1·862 ± 0·138
	3	5	2·402 ± 0·083*†	4·221 ± 0·116*†	1·819 ± 0·113*
Inferior	1	14	1·613 ± 0·239	3·593 ± 0·384	1·980 ± 0·264
	2	5	1·990 ± 0·237*	3·964 ± 0·236*	1·974 ± 0·143
CK class					
	1	15	1·608 ± 0·237	3·595 ± 0·318	1·986 ± 0·255
	2	12	1·856 ± 0·337*	3·711 ± 0·517	1·854 ± 0·274
	3	9	2·069 ± 0·294*†	3·980 ± 0·253*	1·911 ± 0·144
	4	6	2·317 ± 0·148*†	4·125 ± 0·190*	1·808 ± 0·109*

For definition of clinical, electrocardiogram, and CK classes see Methods.

Footnote: Data are analysed by logarithmic transformation to compare geometric means, and are given as mean ± SD of log 10 points, counts, or counts/point.

*Indicates $P < 0·05$ compared with respective class 1.

†Indicates $P < 0·05$ compared with respective preceding class, where this is not class 1.

CORRELATION OF COMPUTED 'INFARCT ACTIVITY', WITH CLINICAL, ELECTROCARDIOGRAM, AND CK CLASSIFICATION

Only the LAO projection was used in this analysis. Table 3 shows that the *computed infarct area* (number of points showing 'infarct activity') differed significantly between all clinical classes, all electrocardiographic classes of severity, and all CK classes. If *total computed infarct activity* (total number of counts) is considered, the discrimination is not quite so good though the differences between clinical classes and between electrocardiographic classes of severity remain significant. The average uptake *density* (counts/point) did not differ significantly between any adjacent clinical, electrocardiogram, or CK class. The average count density was in fact significantly less in anterior electrocardiogram class 3 compared with class 1 and in CK class 4 compared with class 1.

Discussion

The accuracy of any assessment of infarct size from surface scintigraphy will be related to the density of the uptake over the infarct relative to the surrounding area and to the sharpness with which it can be defined. Precise constancy of recording technique is obviously essential. The first part of this study is concerned with establishing optimum conditions for measuring infarct size, using 99^{m} Tc polyphosphate (as distinct from the more commonly used 99^{m} Tc pyrophosphate).

Background blood pool activity declined rapidly after injection of the isotope. Infarct/bone uptake ratio also declined, partly because blood pool activity will contribute to total activity measured over the infarct. The infarct edge, however, was more sharply defined at the later time, probably also because of declining blood pool and therefore background activity. We therefore chose to use the later time (2½ hours) after isotope injection. Scintigrams were compared on day 1 and on day 2 (or 3) after the clinical onset of the myocardial infarct. Both infarct/bone uptake ratio and the sharpness of the infarct edge were better on day 2 (or 3) than on day 1. This finding is in keeping with the observation of improved image quality obtained after the first 24 hours by other workers (Bonte *et al.*, 1975) using Tc pyrophosphate and probably indicates increasing tracer concentration in the infarct over the first few days.

We recorded 99^{m} Tc polyphosphate scintigrams 2½ hours after injection on day 2 (or 3) in patients with transmural infarcts. Subjective grading of infarct severity from scintigrams in terms of infarct area, or density, or a combination of area and density correlated poorly with the other clinical, electrocardiographic, and enzymatic criteria of infarct severity. This remained true whether a single left anterior oblique projection was used or a combination of the three projections. With the aid of computer analysis, however, a highly significant correlation was demonstrated with all the different clinical, electrocardiographic, and enzyme criteria.

This study establishes a relation between myocardial infarct size and the size of the image of the infarct obtained from surface scintigrams in man.

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Uhl's anomaly

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SUMMARY Uhl's anomaly of the heart is a rare condition. Another well-documented case is presented with a review of the published reports outlining the main clinical features and the bad overall prognosis. Right atriotomy should be avoided if closure of the atrial septal defect is attempted.

In 1952, Uhl reported a previously undescribed congenital malformation of the heart. This consisted of an almost total absence of the myocardium of the right ventricle. In the same year, Castleman and Towne (1952) described the case of a woman with a paper-thin right ventricle the volume of which was estimated to be 5 times that of the left ventricle.

In both instances, the predominant feature was the very thin-walled and enlarged right ventricle; this was unlike the case previously reported by Osler as 'parchment heart' in which both ventricles were found to be extremely thin (Segall, 1950).

Few additional cases have since come to light (Taussig, 1960; Arcilla and Gasul, 1961; Reeve and Macdonald, 1964; Cumming *et al.*, 1965; Neimann *et al.*, 1965; Perrin and Mehrizi, 1965; Froment *et al.*, 1968; Kinare *et al.*, 1969; Aherne, 1973; Côté *et al.*, 1973; Perez Diaz *et al.*, 1973; French *et al.*, 1975; Haworth *et al.*, 1975) and we wish to present another patient with this rare condition.

Case report

A 19-year-old Maltese man was admitted for cardiac investigation. He was the youngest of a family of 9, all of whom were healthy. At the time of pregnancy his mother was aged 40. Both pregnancy and parturition were uneventful. At 1 week he was cyanosed particularly on crying. At the age of 9 years he was more cyanosed, clubbed, and of a gracile build. The heart was 'quiet' to palpation and pulmonary closure was delayed. The haemoglobin was 15·4 g/dl. He grew to adult size, enjoying normal schooling and playing football until the age of 15 years. From then onwards he complained of dyspnoea and tiredness on exertion. He suffered from occasional chest pains and lost consciousness three times during physical effort. His haemoglobin had risen to 17·5 g/dl and ectopic rhythm

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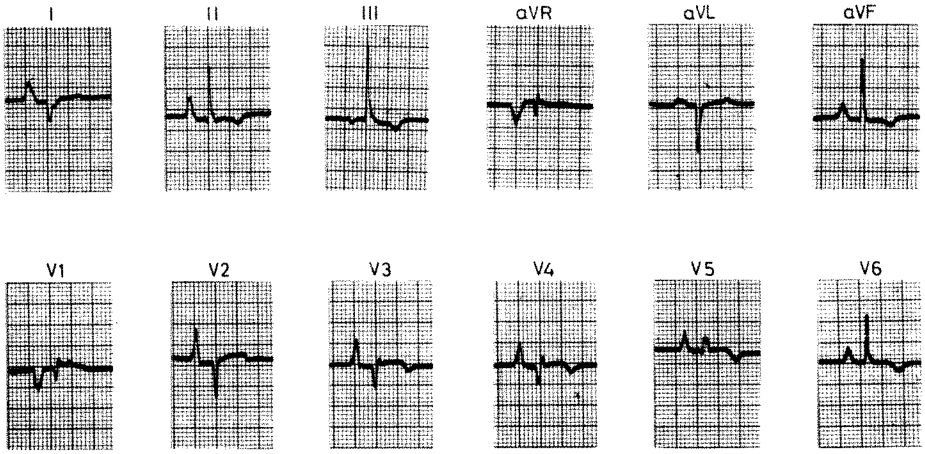

Fig. 1 *Electrocardiogram showing right axis deviation, prominent P waves in leads I, II, and V2 to V4, large negative P waves in V1, and Q waves in V1 to V4.*

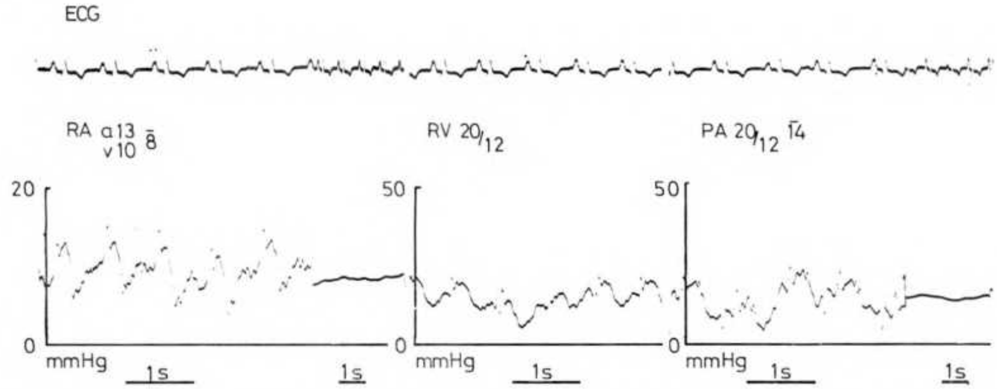

Fig. 2 *Right-sided pressures showing the dominant* a *wave in the right atrium. This is transmitted to the low right ventricle and pulmonary artery pressures.*

activity was also noted. A chest *x*-ray film showed an enlarged heart and the clinical diagnosis of Ebstein's disease was made (see Fig. 3a).

On admission, the jugular venous pressure was raised with a dominant *a* wave. The cyanosis and clubbing were more evident and the haemoglobin was 23·4 g/dl, with a packed cell volume of 73 per cent.

Electrocardiography (Fig. 1) showed right axis deviation and Qr complexes in V2 to V4. There were tall P waves in leads I, II, and V2 to V4, and deep inverted P waves in V1 of greater amplitude than the ventricular complex. Echocardiography showed a dilated right ventricular cavity in comparison with the much smaller left ventricle. The pulmonary valve was clearly seen to open during diastole.

Cardiac catheterisation disclosed arterial desaturation (73%) with right atrial, right ventricular, and pulmonary arterial saturations ranging between 52 and 60 per cent. The pressures (Fig. 2) showed similar contours in the three right-sided areas. The dominant right atrial *a* wave was transmitted into the low pressure right ventricle and pulmonary artery.

Endocardial potentials showed a normal transition of ventricular to atrial complexes, thus excluding a displaced tricuspid valve. This was

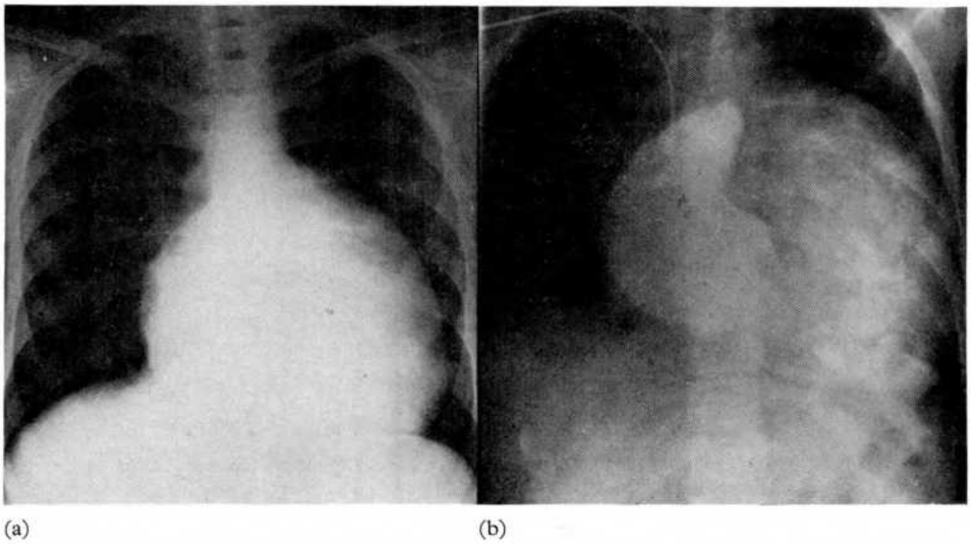

Fig. 3 (a) *Plain chest* x-*ray film on the left. There is obvious cardiomegaly with pulmonary oligaemia.* (b) *On the right, contrast material filling the enlarged right atrium with normally placed tricuspid valve.*

confirmed by angiography (Fig. 3b). Contrast was seen to enter a conspicuously dilated right ventricle during atrial contraction and to stagnate within the right ventricle which did not appear to contract. There was no visible contrast in the left atrium.

As a result of these findings and the gradual deterioration of the patient it was felt that surgical closure of the presumed patent foramen ovale or atrial septal defect was indicated.

At operation a grossly dilated right ventricle was found showing paradoxical pulsation. The right atrium was relatively thick-walled and enlarged. Cardiopulmonary bypass with moderate hypothermia to 30°C was instituted and through a posteriorly placed right atriotomy a 3 × 2 cm secundum atrial septal defect was closed with a continuous suture. Rewarming and right atrial closure were uneventful; total perfusion time was 40 minutes with aortic cross-clamping time of 10 minutes. Half an hour later, during closure of the chest wall, there was a sudden drop in arterial systolic pressure from 110 to 50 mmHg, with a

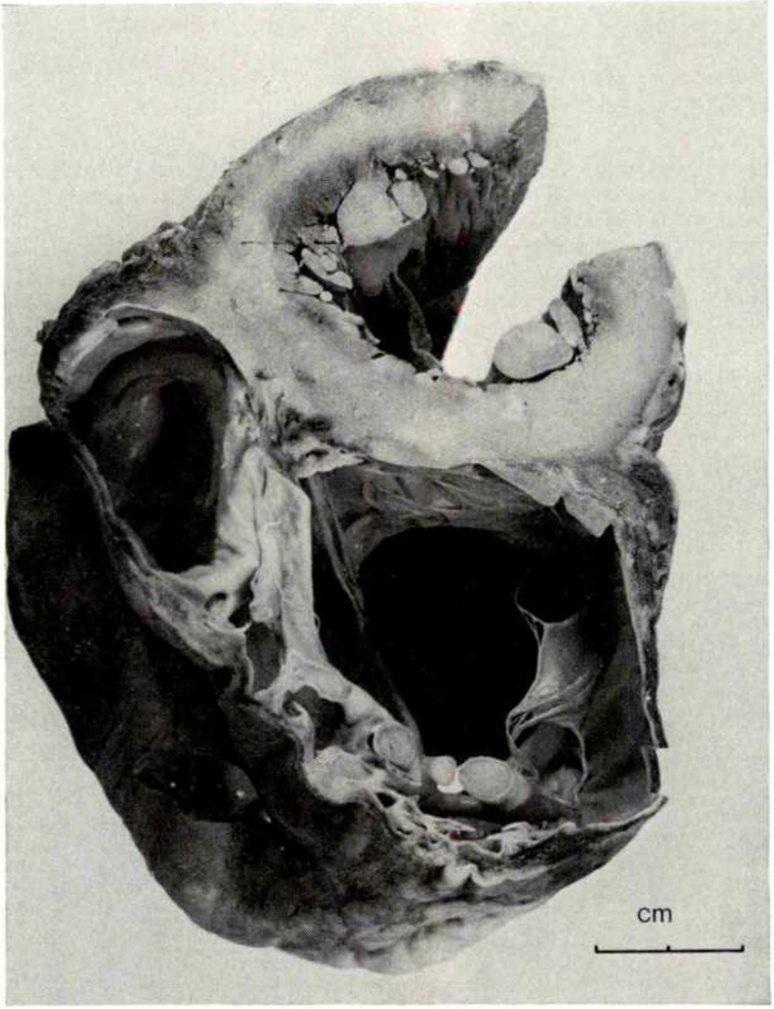

Fig. 4 *The heart has been cut transversely through both ventricles and the upper part is seen from below. The left ventricle and part of the mitral valve are seen at the upper right. The remainder of the picture is occupied by the thin-walled and enormously dilated right ventricle, the cavity of which is crossed by a moderator band. The pulmonary outflow tract is seen in the centre left of the picture and the normally placed tricuspid valve leaflets and papillary muscles at the lower right.*

change in rhythm to atrial fibrillation. Despite several attempts at DC conversion, the arrhythmia persisted and the left ventricle then fibrillated. Further resuscitative measures failed.

NECROPSY FINDINGS

The heart weighed 435 g. Its venous and arterial connections were normal and the ductus arteriosus

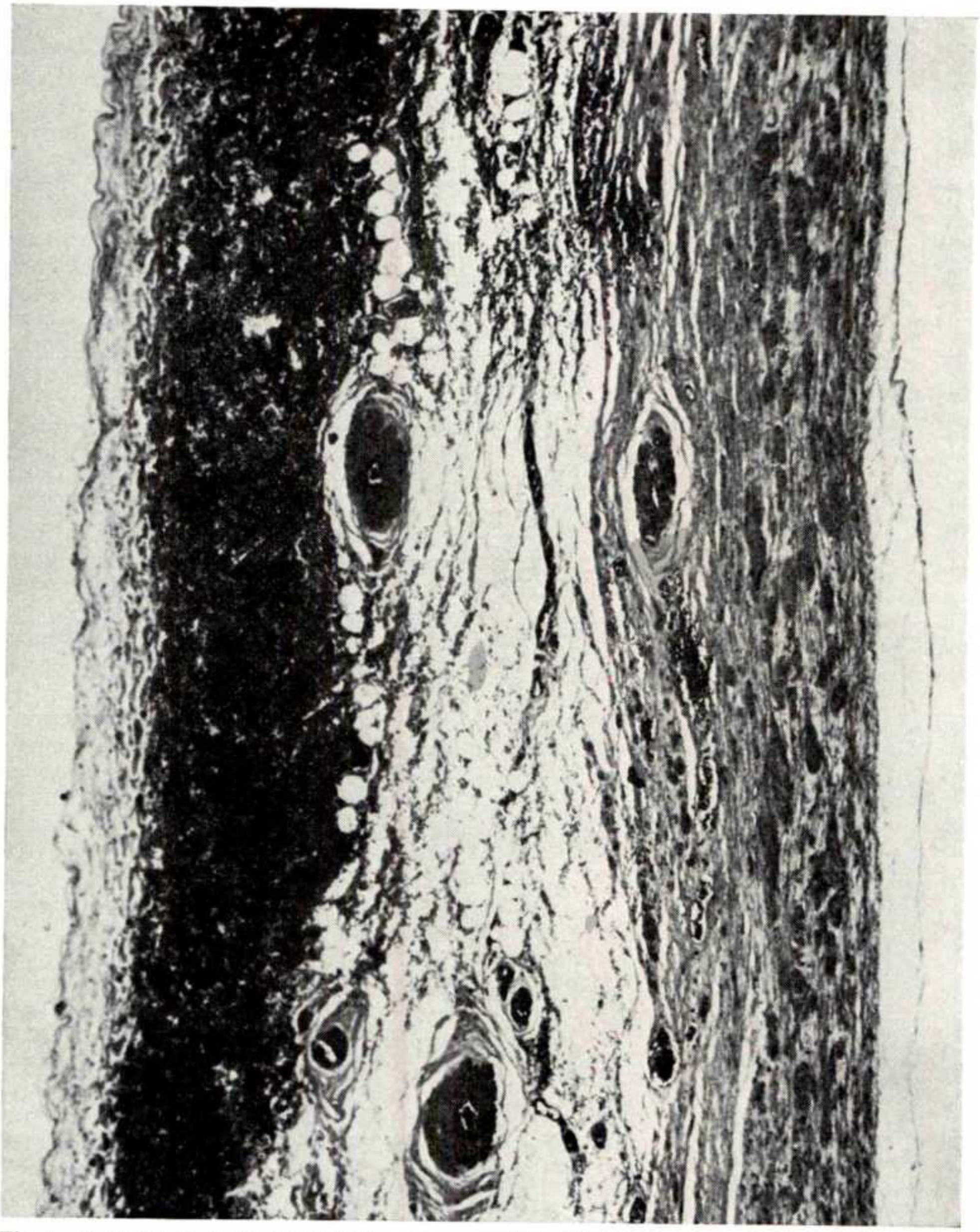

Fig. 5 *A section of the free wall of the right ventricle showing (from left to right) pericardium and fatty epicardial tissue with areas of operative haemorrhage and several thick-walled blood vessels. This is in direct contact with the thickened endocardium with no intervening muscular layer. The muscle bundles visible to the extreme right of the picture are hypertrophied endocardial smooth muscle and are not myocardial fibres.*

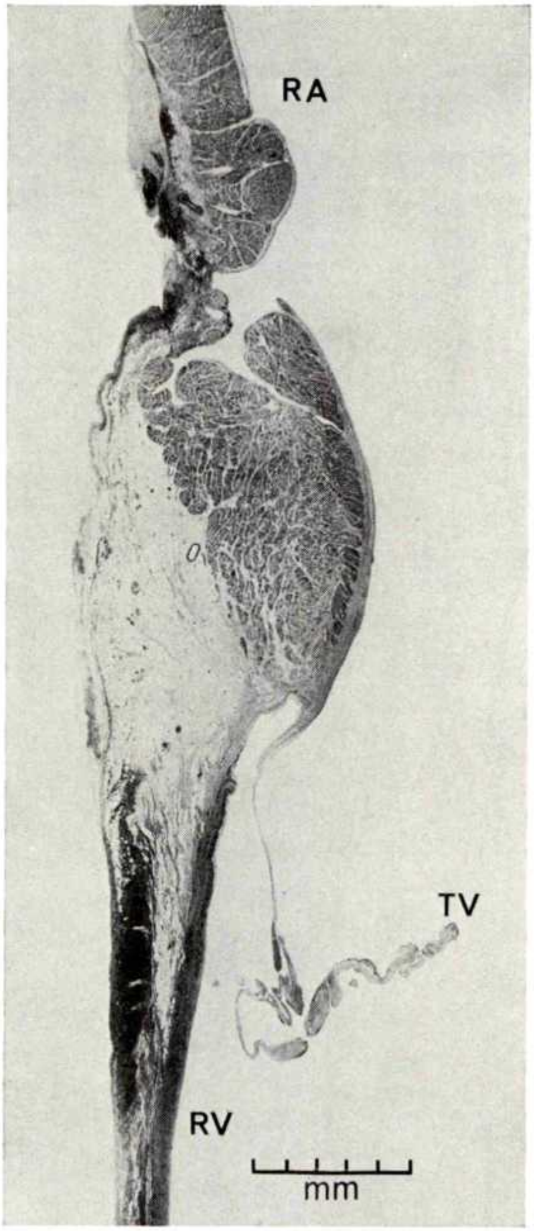

Fig. 6 *A section through the tricuspid valve ring showing the greatly hypertrophied right atrium (RA) above and the thin right ventricular wall (RV) below. The tricuspid valve (TV) is normally sited.*

was closed. The right atrium was a large chamber (7 × 6 × 5 cm) with a hypertrophied and trabeculated wall which measured up to 5 mm in thickness. The tricuspid valve leaflets were normally positioned and were inserted into a fibrous and muscular ring 15 cm in circumference. Just below this, the right ventricle decreased abruptly in thickness and the greater part of its free wall measured only 2 mm in thickness, though the areas adjacent to the interventricular septum were thicker. The right ventricular cavity was enormously dilated (11 × 8 × 7 cm) and was lined by thickened endocardium (Fig. 4). Its cavity was crossed by a moderator band and several narrower bands of fibrous tissue, but no mural thrombus was present. The pulmonary valve was normal. The chambers and valves of the left side of the heart were normal and the coronary arteries were normal in size and position, with the right coronary artery slightly smaller than the left. The sutures were all intact.

Microscopy of the free wall of the right ventricle showed cardiac muscle to be limited to small areas close to the interventricular septum and the tricuspid valve. The thin membrane which surrounded the greater part of the chamber contained no striated muscle and from within outwards consisted of (i) endothelium, (ii) a thickened fibrous endocardium containing numerous bundles of hypertrophied smooth muscle cells and an increase in elastic tissue, (iii) fatty epicardial tissue, and (iv) visceral pericardium (Fig. 5). The epicardial layer contained prominent thick-walled blood vessels. Sections from the right atrium showed hypertrophy of the myocardium (Fig. 6) but no alteration in the endocardium. Sections from the left heart showed no special features.

The endocardial changes were of the type associated with long-standing cardiac dilatation (Fisher and Davies, 1958). The muscular thickening of the epicardial vessels can probably be attributed to the same cause since similar vessels have been described in the adventitial layer of thoracic aortic aneurysms (Pomerance *et al.*, 1977).

Discussion

Uhl's anomaly is rarely encountered and should not be confused with isolated right ventricular hypoplasia (Sackner *et al.*, 1961; Van der Hauwaert and Michaelson, 1971; Haworth *et al.*, 1975). Common to all cases of Uhl's anomaly described is the extremely thin and enlarged right ventricular wall which contains little if any myocardium. This is in contrast with the small right ventricular cavity and normal wall thickness found in cases of right ventricular hypoplasia. From the Table reviewing the published cases of Uhl's anomaly it can be seen that the sex incidence was equal and that ages at presentation ranged from 1 day to 57 years. Of the 18 cases reviewed here cyanosis was noticeable in

Table *Salient features in patients with Uhl's anomaly: review of published reports*

Author	*Year of publication*	*Age/ sex*	*Presenting features*	*Other signs*	*Age and cause of death*	*Post mortem*	*RV*	*RA*	*LV*	*Coronary arteries*	*ASD/ FO*	*Surgery*
Uhl	1952	7/12 F	Tachypnoea	Cyanosis, oedema, cardiomegaly	8/12 CCF	Yes	Thin, large thrombus	Large	N	N	None	None
Castleman and Towne	1952	24y F	Dyspnoea, ectopic beats, atrial flutter, AV block, chest pain	Raised JVP, oedema, cardiomegaly	25y CCF	Yes	Thin, large thrombus	Large Thin	N	N	None	None
Taussig	1960	6y M	Dyspnoea, reduced exercise tolerance	CCF, cyanosis, cardiomegaly, 1° AV block	6y postop	Yes	Normal size	Large	N	N	ASD	Pott's, later closed
Arcilla and Gasul	1961	5/12 M	Tachypnoea	Cardiomegaly	12/12 CCF	Yes	Large paper-thin	Large	Large	?	FO	None
Reeve and Macdonald	1964	47y F	Dyspnoea, SVT, chest pain	Cyanosis, cardiomegaly	47y subarachnoid haemorrhage	Yes	Large	Large	N	N	FO	None
Cumming *et al.*	1965	7/12 F	Dyspnoea	Cyanosis, cardiomegaly	7/12 postop	Yes	Large	Large	N	N	FO	Glenn
Neimann *et al.*	1965	4d F	Tachypnoea	Cyanosis, cardiomegaly, hepatomegaly	5 d hypothermia	Yes	Large thin	Large	LVH	N	ASD	None
Perrin and Mehrizi	1965	10/12 M	Oedema	Cyanosis, raised JVP, cardiomegaly	13/12 CCF	Yes	Large paper-thin	Large Thin	N	N	None	None
Gould *et al.*	1967	57y M	Chest pain	Hepatomegaly, no cardiomegaly	66y leukaemia, renal failure	Yes	Large paper-thin	N	LVH	N	None	None
Froment *et al.*	1968	19y M	Dyspnoea	Cardiomegaly	19y postop	Yes	Large thin thrombus	Large 2 cusps	N	N	None	Exploratory
,	„	26y M	VT	Cardiomegaly	26y arrhythmia	Yes	Large thin thrombus	Large 2 cusps	?	?	?	None
Kinare *et al.*	1969	5y F	Dyspnoea	Cyanosis cardiomegaly	5y postop	Yes	Large paper-thin	Large	N	N	None	Exploratory
Aherne	1973	7/52 F	Oedema	CCF, cardiomegaly	10/12 CCF	Yes	Large thin	Large	N	N	None	None
Côté *et al.*	1973	19h F	Tachypnoea	Cyanosis, gallop, cardiomegaly, hepatomegaly	2½d respiratory distress	Yes	Large thin	Large thin	N	N	ASD	None
Perez Diaz *et al.*	1973	4/12 M	Dyspnoea	Cyanosis, CCF, cardiomegaly	4/12 CCF	Yes	Large thin	Large	N	N	None	None
French *et al.*	1975	14y F	Diminished exercise tolerance, AV dissociation, nodal rhythm	Cyanosis, cardiomegaly	Alive	—	Large	Large	Large	?	ASD	ASD closed
Haworth *et al.*	1975	1d M		Cyanosis, cardiomegaly, hepatomegaly	4 days not known	Yes	Large thin	Large	?	?	FO	None
Vecht *et al.*	present report	19y M	Dyspnoea, chest pain, ectopics	Cyanosis, cardiomegaly	19y postop	Yes	Large paper-thin	Large	N	N	ASD	ASD closed

RV, right ventricle; RA, right atrium; LV, left ventricle; ASD, atrial septal defect; FO, foramen ovale; CCF, congestive cardiac failure; N, normal; JVP, jugular venous pressure; SVT, supraventricular tachycardia; LVH, left ventricular hypertrophy; VT, ventricular tachycardia.

12 cases. Four patients had patent foramen ovales and 5 others had atrial septal defects. In some cases cyanosis was present without an obvious intracardiac shunt.

Right ventricular thrombus was found in 4 cases and arrhythmias were described in 6 patients. Four patients complained of chest pain and effort syncope was encountered in 2 cases. Non-specific systolic murmurs were frequently audible. Seventeen of the patients succumbed and only 1 survived operation (closure of atrial septal defect).

Electrocardiography characteristically showed large P waves in lead II, with diminished right ventricular potentials. Chest radiography invariably demonstrated an enlarged cardiac shadow. Specific echocardiographic features consisted of an enlarged right ventricular cavity, delayed tricuspid valve closure, and diastolic pulmonary valve opening, allowing differentiation from Ebstein's anomaly which closely resembles this condition.

Additional defects have been described in association with Uhl's anomaly. They include dysplasia of the tricuspid valve, pulmonary atresia, and persistent ductus arteriosus (Neimann *et al.*, 1965; Côté *et al.*, 1973; Haworth *et al.*, 1975). These rare defects were seen infrequently.

The pulmonary circulation in Uhl's anomaly is entirely maintained by right atrial contraction. This is recognisable at angiography and from the similar pressure contours seen in the right-sided chambers. The tricuspid valve is not displaced as in Ebstein's syndrome; the left ventricle and the left atrium are usually normal as are the coronary arteries. Fibroelastosis was seen in a few cases. Surgical management has included Glenn and Potts procedures with unacceptable results. It has been suggested that before operation right heart function should be assessed by temporary balloon occlusion of the defect (Van der Hauwaert and Michaelson, 1971) though this is not always possible (Haworth *et al.*, 1975) and was not attempted in our case. Closure of an atrial septal defect may offer some benefit and was performed in our case, though death ensued after the onset of atrial fibrillation. It is assumed that this was related to the right atrial incision and we suggest that the surgical approach might be via a right ventricular incision with closure of the atrial septal defect through the tricuspid valve. Thus an atrial incision would be avoided.

We wish to thank Dr E. M. M. Besterman and Mr L. L. Bromley for allowing us to study their patient.

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Maximal supine exercise haemodynamics after open heart surgery for Fallot's tetralogy

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SUMMARY Maximal supine exercise studies at the time of heart catheterisation were performed one to five years after open heart surgery for Fallot's tetralogy on 29 subjects 6 to 16 years of age. During exercise right ventricular systolic pressure exceeded 50 mmHg in all but 2 subjects, and end-diastolic pressure increased to over 15 mmHg in 10 subjects. Pulmonary artery peak systolic pressure was abnormal in 5 patients. Maximal exercise cardiac index was below the normal range in only 2 subjects, but below the mean for normals in 80 per cent of the patients. Only 3 patients had clinical exercise performances below the 3rd centile of normal subjects using a maximal upright bicycle exercise test, and only 1 subject was below the normal range for endurance time on the Bruce treadmill test. The patients in this series performed better than those in other series, possibly because of their younger age at operation, the use of a large control series of normal subjects taken from a clinic population, the willingness of the patients to work to near exhaustion, and previous encouragement of the patients to become normally active children.

There are several published reports of haemodynamic studies after open heart surgery in patients with Fallot's tetralogy, and some of these include exercise data (Gotsman, 1966; Shah and Kidd, 1966; Bristow *et al.*, 1970; Epstein *et al.*, 1973; Bjarke, 1975; Mocellin *et al.*, 1975, 1976). The following report differs from these others in one or more ways: studies were made during exercise on a large number of subjects including those with and without various residual defects; measurements were made during maximal exercise; haemodynamic measurements included intracardiac pressures, arterial and mixed venous blood gas tensions, and cardiac output (by indicator dilution method), during submaximal and maximal exercise in the supine position. Clinical exercise testing used both maximal treadmill and bicycle exercise. The subjects were younger than those in other series and comparative data were available for a large series of normal children studied in the same manner.

Subjects

The patients studied were 29 children who had had open heart operations at ages ranging from 5 to 14 years (mean 8·2). All but 2 were cyanotic at the time of operation. Of the 29 (34%), 10 had had a previous shunt operation. An outflow tract patch had been inserted in 11 of the 29 patients (38%), and in 7 this extended to the pulmonary artery bifurcation. The catheterisation studies were carried out 1 to 5 years after operation (mean age 11·3 years, range 6 to 16). The exercise studies were performed at the time of diagnostic postoperative haemodynamic assessment.

The patients were divided into 5 subgroups: (1) those in the 'repaired' group with a closed ventricular septal defect and a peak gradient from right ventricle to pulmonary artery of 20 mmHg or less (11 patients); (2) those with a closed ventricular septal defect but a peak gradient of over 20 mmHg (7 patients); (3) those with a small residual ventricular septal defect and pulmonary blood flow 1·25 times systemic flow or less (4 patients); (4) those with a 'poor repair' with a large ventricular septal defect and also an outflow gradient of over 20 mmHg (5 patients); and (5) 2 patients with complete atrioventricular block, both with a permanent pacemaker set at 80 beats/minute, but otherwise a good surgical result.

Methods

The haemodynamic studies were carried out after an overnight fast 45 minutes after diazepam 5 mg

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or pethidine 25 mg. Catheters were introduced percutaneously into a cubital or femoral vein, and the brachial artery was cannulated with a Cournand needle. After the exercise studies most subjects also had right and left ventriculograms. Control measurements were obtained 5 minutes after the subject's feet had been placed on and strapped to the ergometer pedals. A calibrated Elema electric ergometer was used with pedalling rates of 60 rpm for submaximal exercise and 70 to 75 rpm for maximal exercise. Subjects exercised for 3 minutes at about 5 kpm/min per kg body weight, rested 3 minutes, then exercised for 3 minutes at 8 to 12 kpm/min per kg, rested again for 5 to 10 minutes, and then exercised at 15 to 25 kpm/min per kg until they could no longer sustain the pedalling rate. The final work load (chosen on the basis of a clinical exercise test and the response to the previous loads) usually exhausted the subjects in 90 to 180 seconds. Oxygen uptake was not measured but the submaximal loads would have required about 14 and 25 ml/min per kg of oxygen, and the maximal loads if done aerobically 32 to 55 ml/min per kg of oxygen. Five of the 29 subjects did not exercise at a maximal work load as they were studied before maximal exercise testing was used routinely in the catheterisation laboratory.

During exercise pulmonary and brachial artery pressures were recorded using a Statham P23Db transducer, and immediately after the maximal exercise the catheter was withdrawn from the pulmonary artery to the right ventricle. Cardiac output was measured using indocyanine green dye and a Waters densitometer, and a dynamic calibration method (Shinebourne *et al.*, 1967). For the few patients with significant left-to-right shunts, pulmonary blood flow was calculated from the indicator dilution curves using the forward triangle method (Hetzel *et al.*, 1958), the left-to-right shunt was estimated using the method of Carter *et al.* (1960), and systemic output was derived from these two measurements. During the third minute at each exercise level, blood was withdrawn from the pulmonary and brachial arteries for P_{O_2} and pH determinations. Percentage oxygen saturation was derived using the standard oxyhaemoglobin dissociation curve.

Clinical exercise testing was carried out on the upright bicycle ergometer and on the treadmill in a clinical laboratory. On the upright bicycle ergometer, the subjects exercised at 5 to 8 kpm/min per kg for 6 minutes, and at 9 to 13 kpm/min per kg for 6 minutes, after which the work load was increased by 100 kpm/min each minute until exhaustion occurred. Maximal work was expressed as kpm/min per kg and compared with centiles for normal children established for this laboratory (Cumming, 1977a). Subjects also performed the Bruce treadmill test and the maximal work times were compared with centiles for normal children established for this laboratory (Cumming *et al.*, 1978). Normal centile values for both treadmill and bicycle exercise were established from exercise tests in over 500 children who did not have heart disease and who were seen in a cardiac clinic over a 10-year period.

Results

The haemodynamic results are shown in Fig. 1 to 8, with shaded areas to show the normal range (mean ±2 standard deviations) for 60 children studied over the same period of time as the tetralogy patients. None of the patients developed an arrhythmia during exercise at catheterisation. Subject 6 subsequently developed exercise induced ventricular tachycardia with treadmill testing, as has been reported by James *et al.* (1976) in patients after operation for Fallot's tetralogy.

The peak right ventricular pressure increased during exercise in all subjects and in only 3 subjects was the pressure during exercise less than the normal maximal value of 48 mmHg (Fig. 1). The peak right ventricle to pulmonary artery pressure gradient increased during exercise in all subjects, and in all but 4 subjects was abnormal during exercise (Fig. 2). There was one very high value in the 'poor repair' group, and 5 of 7 subjects with residual pulmonary stenosis had peak gradients of over 50 mmHg with exercise. There was a strong correlation between the resting and exercise right

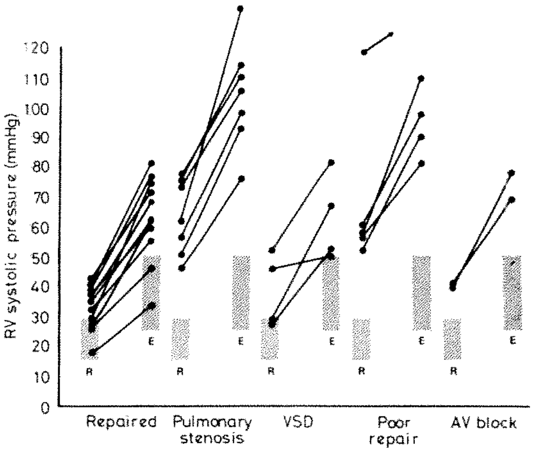

Fig. 1 *Peak systolic pressure in the right ventricle at rest (R) and immediately after exercise (E). Normal range is shown by hatched columns.*

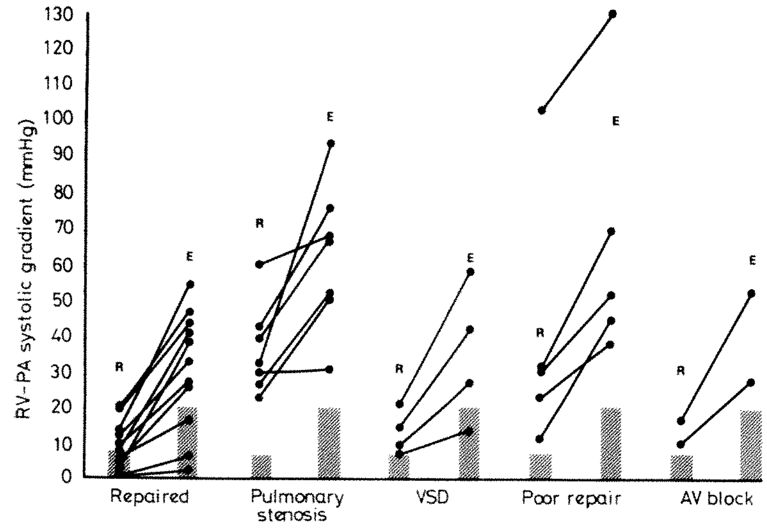

Fig. 2 *Peak right ventricular systolic pressure minus peak pulmonary artery systolic pressures at rest (R) and immediately after exercise (E). Normal range (up to 8 mmHg rest and 20 mmHg after exercise) is shown.*

ventricular systolic pressures and right ventricle to pulmonary artery gradient though there were a few exceptions (2 patients with resting gradients of 2 and 32 mmHg had exercise gradients of 40 and 94 mmHg, respectively).

Right ventricular end-diastolic pressure increased abnormally in all 5 subjects in the 'poor repair' group, in both patients with atrioventricular block, and in 3 of the 7 patients with resting gradients over 20 mmHg (Fig. 3). Several other patients had an abnormal right ventricular end-diastolic pressure at rest but did not show any major increases on exercise. There was a low order correlation between the exercise right ventricular end-diastolic pressure and the right ventricular systolic pressure.

Fig. 4 shows the cardiac output at submaximal work loads expressed as the increase in output above the resting value. Eighty-four per cent of the 45 values fell below the mean established for the normal subjects, but only 6 (13%) were more than 2 standard deviations below the mean and these low values occurred in 3 patients. Values above the mean for the normals were observed 7 times, though none was more than 1 standard deviation

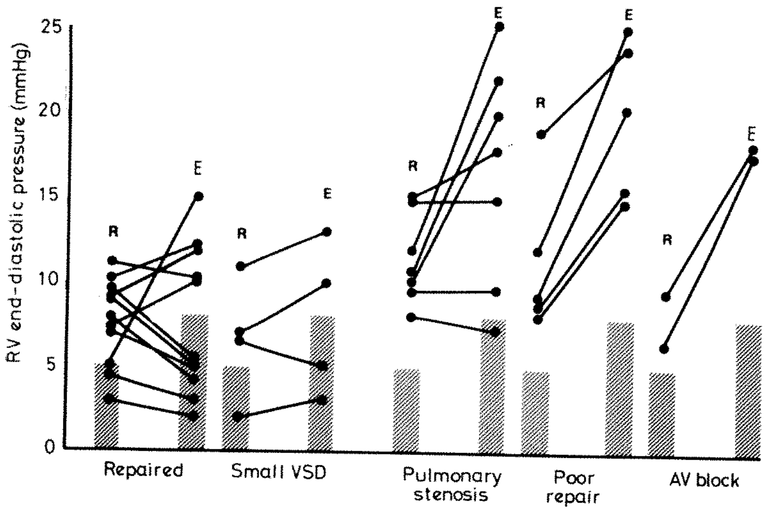

Fig. 3 *Right ventricular end-diastolic pressure at rest (R) and after exercise (E). Normal range (up to 5 mmHg at rest and 8 mmHg during or after exercise) is shown.*

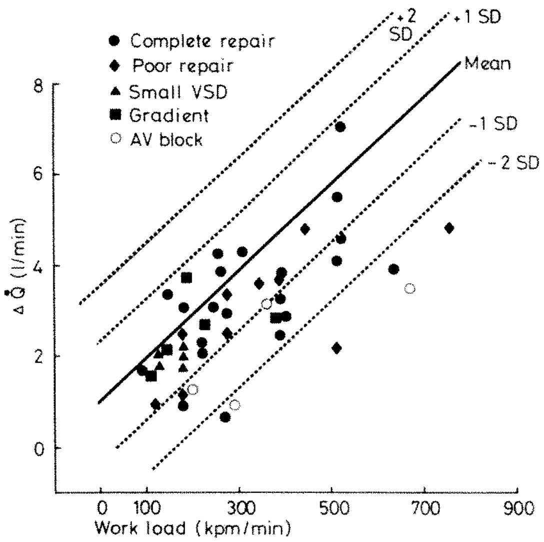

Fig. 4 *Cardiac output increase with submaximal exercise* (*△ Q̇*). *Exercise cardiac output minus resting output in litres per minute plotted against work load in kilopond metres per minute. Regression (solid) line is shown for normal subjects with standard deviations (dotted lines).*

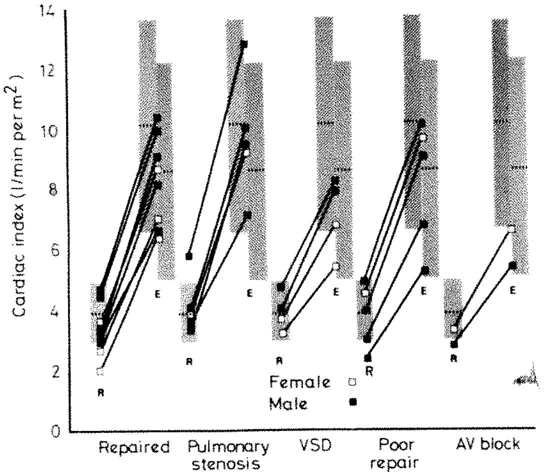

Fig. 5 *Cardiac index in litres/minute per m² body surface area at rest and during maximal exercise. Hatched columns indicate the normal ranges which are the same for boys and girls at rest, but different during exercise: during exercise the normal ranges for boys are shown on the left, and the normal ranges for girls on the right; the dotted lines in these ranges indicate the mean values for the normal group.*

above the mean. Thus, the cardiac output during submaximal exercise was in the lower half of the normal range in most patients.

Resting cardiac index was below 2·9 l/min per m² in 5 subjects (21%) and below the mean of the normal values for this laboratory in 18 subjects (75%) (Fig. 5). Maximal exercise cardiac index (measured in 24 patients) was below the normal range in two subjects, the boy with complete atrioventricular block and one patient with a poor repair. However, maximal cardiac index was below the mean value for normals in 19 of the 24 subjects exercised maximally (79%).

During submaximal supine exercise, stroke volume in normal children usually increases about 10 per cent above resting (Cumming, 1972). The response to maximal exercise is variable, with stroke volume either staying the same, decreasing, or occasionally increasing slightly compared with values for submaximal exercise. Fig. 6 shows the resting stroke volume indices, and the highest values observed during exercise. There was an increase in

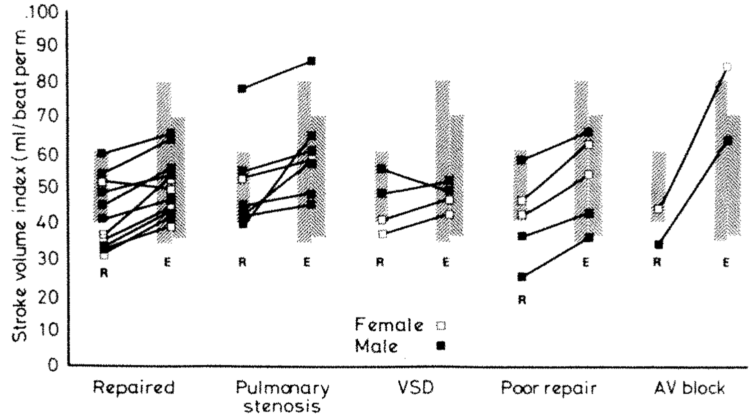

Fig. 6 *Stroke volume index in ml/beat per m² body surface area at rest (R) and during exercise (E). The normal ranges are shown as in Fig. 5.*

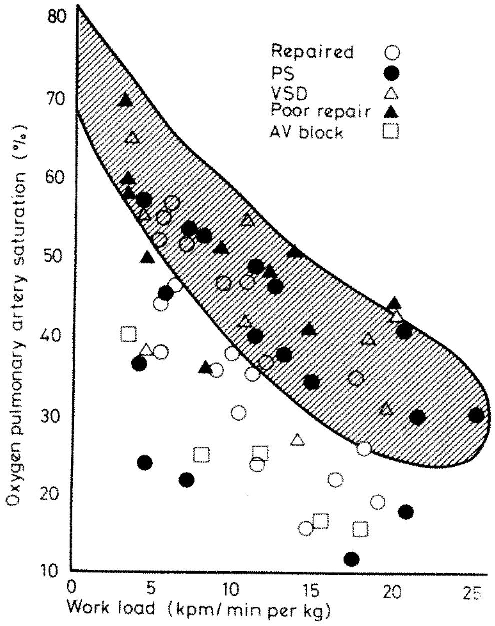

Fig. 7 *Percentage oxygen saturation in pulmonary artery blood during exercise plotted against work load in kpm/min per kg body weight. Hatched area shows normal range.*

stroke volume index with exercise in all except 2 patients. This increase was greatest in the 2 subjects with heart block.

The percentage oxygen saturation in the pulmonary artery blood during exercise is plotted against the work load per kg body weight in Fig. 7. There were some subjects in all patient groups with values below the normal range, including the 2 patients in group 5 with heart block. Some of the patients with left-to-right shunts had values in the high normal range.

The arterial $\mathrm{Po_2}$ values during the maximal exercise performed by each subject are shown in Fig. 8. Relatively low $\mathrm{Po_2}$ values were found in some normal subjects during near maximal supine exercise, the lower limit of normal being 75 mmHg. (When blood is collected 2 or 3 minutes after exercise, most normal subjects, including those with exercise values of 75 to 80 mmHg, have arterial $\mathrm{Po_2}$ values in the range of 90 to 110 mmHg.) In the postoperative Fallot's tetralogy patients arterial $\mathrm{Po_2}$ was below the normal range in 14 of the 28 patients. In 1 subject this was associated with a moderate right-to-left shunt on the indicator dilution curve, but in the other patients no right-to-left shunt was present. In view of the interesting abnormalities in lung function that follow systemic-to-pulmonary shunt operations (Alderson *et al.*, 1975), those patients who had had previous shunt operations are indicated in Fig. 8, but their values were no lower than those without previous shunt operations.

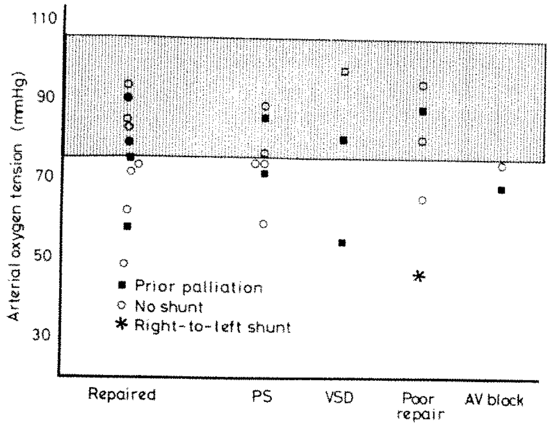

Fig. 8 *Brachial artery* $\mathrm{Po_2}$ *during the maximal supine exercise load performed by the subjects. Shaded area shows the normal range in this laboratory. Patients who had previous systemic-to-pulmonary artery anastomoses are shown by* ■. *Patient* ✻ *was the only one with a right-to-left shunt on the indicator dilution curve.*

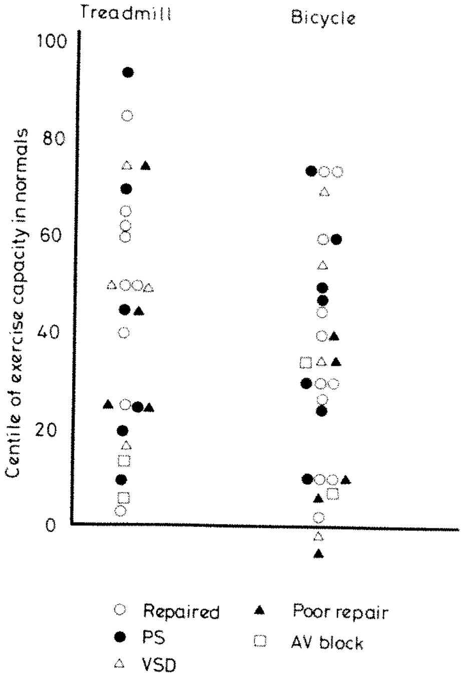

Fig. 9 *Exercise capacity on treadmill (endurance time) and upright (maximal work load) bicycle ergometer. Normal centile values were obtained on clinic patients with innocent heart murmurs.*

The endurance times with the Bruce treadmill procedure and the maximal exercise load with the clinical bicycle ergometer test are shown as centiles of the values established for children without heart disease in Fig. 9. For treadmill exercise the mean centile recorded by the postoperative Fallot's tetralogy patients was 45 per cent, excluding the 1 patient who developed ventricular tachycardia with exercise. Of the 25 subjects tested, 52 per cent had values below the 50th centile, 16 per cent had values approximately on the 50th centile line, and 32 per cent had values above the 50th centile line. The mean maximal heart rate was 189 beats/min (normal mean 202 beats/min).

The maximal work loads completed on the upright bicycle ergometer were above the 50th centile line in 7 subjects (24%), below the 25th centile line in 9 (31%), including 3 (10%) below the 3rd centile line, and no subject had a value above the 75th centile line. The mean centile score was 37 per cent. Mean group centile exercise capacities were lowest in the patients with atrioventricular block and in those with a 'poor repair', but there was considerable overlap. The mean maximal exercise heart rate was 183 beats/min (normal mean 196 beats/min).

Discussion

The systolic pressure increase on withdrawing the catheter from the pulmonary artery to the right ventricle was abrupt and no intermediate zone suggestive of infundibular stenosis was observed. This was in keeping with the right ventricular angiograms which showed wide open outflow tracts in all patients. The pressure changes appeared to be occurring in the area of the pulmonary valve ring, or at the bifurcation of the main pulmonary artery, and while these were the narrowest areas on the angiograms a significant gradient would not have been suspected from viewing the angiograms.

The rise in exercise right ventricular end-diastolic pressures is in agreement with the report of Bristow *et al.* (1970) and might be the result of the previous right ventricular incision, the pulmonary regurgitation, the increase in right ventricular systolic work, or of myocardial hypertrophy and scarring with reduced compliance. The highest end-diastolic pressures were found in the subjects with the most severe haemodynamic disturbances, but the right ventricular end-diastolic pressures did not correlate with exercise cardiac output or the clinical exercise capacity, or the presence of a pulmonary regurgitant murmur.

Peak systolic pulmonary artery pressures might be abnormally high on the basis of branch narrowings, reduced size or compliance of the major pulmonary arteries, inadequacy of the pulmonary vascular bed, possible old thrombotic occlusions, or increased right ventricular stroke volume because of the pulmonary regurgitation, or combinations of the above causes. At preoperative catheterisation, none of the patients had pulmonary hypertension from previous shunt procedures. There was no correlation between the peak pulmonary artery pressure and the clinical grading of the pulmonary regurgitation murmur or the presence of a systemic-to-pulmonary shunt.

The submaximal and maximal exercise cardiac indices and stroke volume indices were clustered in the lower part of the normal range. This is a better response than those reported by Epstein *et al.* (1973) and by Bjarke (1975). The submaximal exercise cardiac outputs were in the lower part of the normal range because of low stroke volumes. The maximal cardiac outputs were low because of low maximal heart rates. The mean maximal exercise heart rate for the supine exercise at the time of catheterisation was only 164 beats/min, and this low figure is believed to be due to three factors. Maximal exercise heart rates in the supine position are normally 10 beats/min below those for the sitting position in adults and in children (Åstrand and Saltin, 1961; Stenberg *et al.*, 1967; Cumming, 1977b). Secondly, maximal exercise heart rates for upright bicycle and treadmill exercise have been reported to be reduced by 20 beats/min in post-surgical patients with Fallot's tetralogy (Epstein *et al.*, 1973; Bjarke, 1975), though the cause is uncertain. Thirdly, the short duration of the maximal exercise used in this study would be an additional factor reducing the maximal heart rate. At catheterisation the duration of the exercise was purposely kept short as this has been one way of obtaining the co-operation of young children. The subjects pedalled until they could not maintain the cycling speed of 70 rpm, and most appeared to have given a true near maximal effort; the only way the duration of exercise could have been increased would have been to reduce the work load used.

A slight fall in arterial oxygen saturation with exercise in postoperative tetralogy patients was reported by Epstein *et al.* (1973) and in the study of Bjarke (1975) P_{aO_2} fell from 99 to 85 mmHg with upright bicycle exercise. The lower values in the patients in this series may have been caused in part by the supine position and the straining that this type of exercise produces. Ventilation perfusion abnormalities have been well documented in postoperative tetralogy patients (Alderson *et al.*, 1975).

Before any reduction in maximal exercise performances of post-surgical patients can be attributed to residual lesions and impaired cardiac function, it is important to exclude non-cardiac factors. Have the patients actually resumed full activity for at least 6 months or longer, or have they held back for one reason or another? Are the patients really being urged to produce maximal efforts in the tests? Is the normal group of subjects roughly comparable with the patients in terms of current physical activity? When comparing the exercise haemodynamic indices or exercise capacity measurements in patients with values in normal subjects, it is important that both groups should have engaged in comparable physical activity. Ideally, both groups should undergo a similar physical training programme 3 or 4 months before a study, and this would include practice sessions with all test procedures. As this was not feasible, the normal values in this study were obtained from a large series of patients who proved to have normal hearts, or nearly normal hearts, when undergoing cardiac evaluation over the same period of time as the postoperative tetralogy patients. The tetralogy patients in this series were all urged gradually to resume normal activities, including full participation in physical education 6 months after operation. The parents were advised to encourage their children to participate normally in all activities while allowing them to seek their own levels of participation rather than to be coached and pushed. Several children, in fact, did take part in demanding sports such as ice-hockey or soccer, but none trained seriously for competitive athletics.

The results of all maximal exercise tests are dependent on motivating the patients to work close to exhaustion, and the skill and determination of exercise technicians is an important factor. All of the subjects in this report finished at least stage 4 of the Bruce test which, if done aerobically, requires an oxygen uptake of 46 ml/min per kg (Cumming *et al.*, 1978). While oxygen uptake was not directly measured, there is no reason to believe that the work efficiency or the anaerobic power of these patients was any greater than in normal subjects.

The patients in this series clearly had higher functional capacities than those in the series of Epstein *et al.* (1973) and Bjarke (1975) ($\dot{V}O_2$ max 25 to 30 ml/min per kg) possibly because the operation was performed at a younger age and the patients had the motivation and opportunity to become normally active. The younger patients of Mocellin *et al.* (1975) also had cardiac output values closer to normal than those reported by Epstein *et al.* (1973) and Bjarke (1975). It is of interest that with clinical exercise testing our patients were able to push themselves to a mean maximal heart rate of 189 beats/min compared with approximately 175 beats/min in the studies of Epstein *et al.* (1973) and Bjarke (1975), and 182 beats/min in the study of James *et al.* (1976). Maximal heart rates of over 190 beats/min, well within the range of normal for maximal heart rate, were recorded during clinical exercise testing in 15 of the 27 patients (2 patients with atrioventricular block omitted). It would be of value to study systematically the response of postoperative tetralogy patients to physical training regimens, but the results reported here indicate that formal rehabilitation programmes are not necessary for these patients to achieve a reasonable functional status.

James *et al.* (1976) found that patients operated on at an earlier age (under age 10) had exercise capacities not significantly different from normal subjects, while those operated on at an older age had subnormal exercise capacities when tested by clinic bicycle ergometry, in agreement with the findings of this report. They also studied 4 older subjects who took part in competitive sports, and found that their exercise capacities were also normal, suggesting that the potential for a normal exercise capacity is present if physical activity is encouraged for these patients.

The mean age of the 10 patients studied by Epstein *et al.* (1973) was 23 years, and of the 18 patients studied by Bjarke (1975) 20 years at operation and 26 years at the time of the postoperative exercise study. The cardiac output response to treadmill exercise in Epstein's series was only slightly below normal, but there was an abnormally low cardiac index at the point when pulmonary artery oxygen saturation fell to 30 per cent. In the study of Bjarke (1975), cardiac outputs during upright bicycle exercise were clustered in the low normal range and 50 per cent of the subjects had values below the normal range in relation to oxygen uptake. In their patients the circulation tended to be hypodynamic in tetralogy patients after operation, even when allowance was made for the reduced maximal exercise capacity and maximal oxygen uptake. In the patients in our series studied during supine exercise, the changes were similar in direction but not in magnitude, so that the exercise cardiac outputs were at the lower end of the normal range but not below. The study of Mocellin *et al.* (1976) involved 21 children, mean age 12 years, operated on at a mean age of 8·5 years, subjects comparable to those in the present report. Mean maximal exercise heart rate was 196 beats/min, the same as normals. The mean maximal $\dot{V}O_2$, stroke volume, and cardiac output were 83 to 89 per cent of mean normal values (based on height), though information was not provided on the normal range or the method of selection of the normal subjects. Presenting our patients' data in the same way and omitting those with a poor repair or atrioventricular block, the mean values for exercise capacity, stroke volume, and cardiac output were also 85 to 90 per cent of the means for normals. The mean $\dot{V}O_2$ max in Mocellin's subjects was determined directly on the bicycle ergometer and was 37 and 34 ml/min per kg for boys and girls, respectively, lower than the predicted values based on treadmill performance in our patients. Mocellin *et al.* indicated that only half of their children took part in school sports, but it is not known whether intense physical activity might be damaging to these children or the only way in which they might achieve a normal functional capacity. All the evidence available suggests that early operation may permit the development of a more normal exercise performance. This may be entirely because of the resumption of normal physical activity during the years of development, but there is also the possibility that cardiac fibrosis, a small left ventricle, and other anatomical abnormalities occur to a greater degree when surgical correction is delayed until late adolescence or adulthood.

Conclusions

(1) After corrective operations for tetralogy of Fallot there are residual haemodynamic abnormalities during exercise, the most striking being high right ventricular systolic and end-diastolic pressures. The high right ventricular systolic pressure occurs in the absence of any angiographic evidence of outflow tract obstruction.

(2) When the corrective operation was done in childhood (age 5 to 13 years), patients with Fallot's tetralogy had exercise capacities in the low normal range during treadmill, upright bicycle, or supine bicycle exercise.

(3) After corrective operations in childhood, the maximal and submaximal exercise cardiac outputs and stroke volumes fall in the lower part of the normal range, but are usually not below normal. The hypodynamic circulation is partially compensated for by a wider arteriovenous oxygen difference.

(4) Patients with a poor repair or with atrioventricular block (with pacemakers) had only slightly less good exercise performances and cardiac output measurements than those with better anatomical results.

All but one of the patients in this series were operated on by Dr Colin C. Ferguson, Department of Surgery, Children's Hospital of Winnipeg.

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Antibodies to Coxsackie B viruses in congestive cardiomyopathy

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SUMMARY Fifty patients with congestive cardiomyopathy have been studied for evidence of previous Coxsackie B virus infection and compared with age- and sex-matched controls who had been admitted to hospital for investigation of other cardiac diseases.

High neutralisation titres ($\geqslant$ 1024) to Coxsackie B viruses were more common among the patients than among the controls. On subdividing the patients according to their length of symptomatic history before study, high titres were more common only in those with a short history ($\leqslant$ 1 year). High titres were more common when there had been a febrile illness at the onset of symptoms.

Endomyocardial biopsies of 18 patients disclosed no evidence of myocarditis, or, in 12 cases, of viral involvement.

Although the evidence remains circumstantial, these results support the theory that Coxsackie B viruses may cause congestive cardiomyopathy and encourage further research into the mechanisms of myocardial cell damage by these viruses.

The causal relation of Coxsackie B viruses to acute myopericarditis is now well established. Though the development of congestive cardiomyopathy occurring after acute viral myocarditis is not well documented, several cases of prolonged cardiac enlargement or dysfunction have been reported (Sainani *et al.*, 1968; Smith, 1970; Levi *et al.*, 1977).

The development of a cardiomyopathy several months after experimental Coxsackie B myocarditis has been observed in mice (Wilson *et al.*, 1969). Microscopically, there was persistent myocardial fibrosis, with small foci of inflammatory cells. After similar infection in hamsters, abnormalities of left ventricular muscle mechanics were still present at a time when histological examination disclosed only scanty focal myocytolysis (Abelmann *et al.*, 1975).

Coxsackie B virus infections are often subclinical, and only a small proportion results in obvious cardiac involvement (Grist *et al.*, 1975). It is therefore possible that chronic congestive cardiomyopathy may develop after an asymptomatic infection. As neutralising antibody titres against Coxsackie B viruses tend to remain raised for many months after acute infection (Grist and Bell, 1974), we have investigated these titres in a group of patients with congestive cardiomyopathy.

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Patients and methods

Fifty patients with congestive cardiomyopathy seen at Hammersmith Hospital between January 1975 and June 1977 were studied. Forty-five of the patients were men and 5 were women. Congestive cardiomyopathy was defined as a chronic disorder of heart muscle of unknown cause or association, characterised by poor systolic function (Goodwin and Oakley, 1972). Cases of specific heart muscle disease or secondary cardiomyopathy were excluded. Though it is recognised that alcohol has an acute depressant effect on left ventricular function, there is no satisfactory evidence that it causes any permanent or irreversible impairment (Goodwin and Oakley, 1972). Patients were not, therefore, excluded from this study if they admitted to abnormally high alcohol consumption. This was the case in 4 patients and the consumption was moderate in a further 4.

The diagnosis in 48 cases was based on haemodynamic evidence at cardiac catheterisation of impaired left ventricular function, together with generalised left ventricular hypokinesia on angiography. In the remaining 2 cases a clinical diagnosis was confirmed *post mortem*. Coronary arteriograms were performed in 15 cases, and were normal in 14. In 1 patient an isolated lesion in the right coronary artery was detected. This was not considered likely to be responsible for diffuse ventricular hypokinesia (Gau *et al.*, 1972; Dash *et al.*, 1977).

Twelve patients gave a history of an acute febrile illness between 1 and 15 months before initial presentation with congestive cardiomyopathy and between 1 month and 13 years before this study. Pericarditis had been reliably diagnosed 2 months previously in 1 such case. There were symptoms suggestive of pericarditis during the acute illness, occurring 9 and 14 months before this investigation in only 2 other cases. In all cases there was an interval of at least 1 month between the acute febrile illness and the apparent onset of cardiac failure.

Patients with other forms of heart disease, admitted for cardiac catheterisation during the same period, were also studied. Those with known infective or inflammatory disease or with abnormal serum proteins were excluded. The closest age- and sex-matched subject was then selected from this group of patients as a control for each patient with congestive cardiomyopathy. The mean age of the cardiomyopathy patients was 43·2 years and of the controls 42·3 years. The geographical origin of the 2 groups was similarly distributed. Among the cardiomyopathy patients 43 were European, 4 were Asian, and 3 were Negro. Of the controls 42 were European, 6 were Asian, and 2 were Negro. Cardiac failure requiring treatment with diuretics was present in 14 of the controls.

COXSACKIE B NEUTRALISATION TESTS

A micro-neutralisation test system was used for the Coxsackie B antibody studies, with a standard volume of 25 microlitres (Bell and Grist, 1970). The stock Coxsackie B1-6 viruses were grown from strains obtained from the Coxsackie reference laboratory (Public Health Laboratory Service, Epsom) and used at a concentration of 100 tissue culture infective doses per microplate well. A continuous line of green monkey kidney cells (VERO) was used as the indicator cell line at a concentration of 25 000 cells per well. Sera were titrated in doubling dilutions from 1:16 to 1:1024. Cell controls and virus back titrations were performed. Each serum was tested for cytotoxicity. The identity of the virus serotypes was confirmed at weekly intervals. Titres to individual B1-6 viruses were determined. In each subject the highest titre to any of the Coxsackie B viruses was also used for analysis. Serial titres were examined in 17 patients in the congestive cardiomyopathy group. In these cases the titres on the second occasion were used for comparison with the control group. Either the χ^2 test with Yates' correction or the Fisher exact test were used for statistical evaluation of the results.

CARDIAC BIOPSIES

In 18 of the patients with congestive cardiomyopathy, transvenous endomyocardial biopsies (Konno and Sakakibara, 1963) were obtained from the right ventricle by one of us (C.M.O.) during cardiac catheterisation. These were examined histologically. In 12 cases standard isolation techniques in tissue culture of primary monkey kidney cells were used to detect infectious virus in the biopsy material and serial sections taken from the biopsies were examined by electron microscopy for the presence of virus particles.

HLA ANTIGENS

HLA typing was performed on the lymphocytes of 20 of the cardiomyopathy patients (Sachs, 1976).

Results

VIRAL ANTIBODIES

Titres $\geqslant$ 1024 to all the individual Coxsackie B viruses except B_6 were more common in the congestive cardiomyopathy patients than controls; but for no type were numbers sufficiently great to reach statistical significance. High titres to Coxsackie B_6 were not encountered in either group. When the Coxsackie B group was taken as a whole, titres $\geqslant$ 1024 were found in 15 patients with congestive cardiomyopathy compared with 1 control ($\chi^2 = 12{\cdot}57, P < 0{\cdot}0005$, Fig. 1).

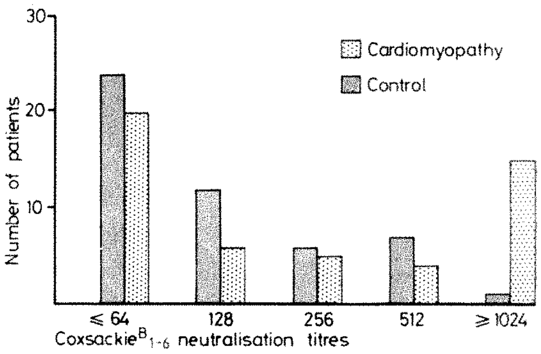

Fig. 1 *The frequency of neutralisation titres to Coxsackie B viruses for the patients with primary congestive cardiomyopathy and for the control patients. For each patient the highest titre to any Coxsackie B virus is taken. Titres* $\geqslant$ *1024 are more common in the cardiomyopathy patients* ($\chi^2 = 12{\cdot}57, P < 0{\cdot}0005$).

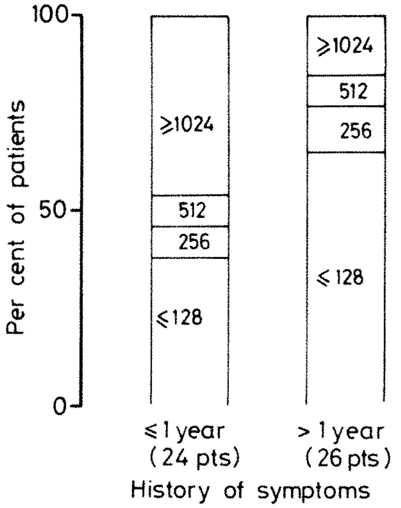

Fig. 2 *The frequencies of the highest titre to any Coxsackie B virus in 50 patients with a primary congestive cardiomyopathy depending on the length of symptomatic history before the virological study. Titres ⩾ 1024 are more common when there is a short history of symptoms ($\chi^2 = 4{\cdot}42, P < 0{\cdot}05$). It is only in this group that high titres are more common than in the control patients ($\chi^2 = 11{\cdot}79, P < 0{\cdot}001$).*

The cardiomyopathy patients were divided into 2 groups, depending on whether the study was performed within one year of the onset of symptoms or later. There was a greater proportion with titres ⩾ 1024 in the group with the shorter history ($\chi^2 = 4{\cdot}42, P < 0{\cdot}05$, Fig. 2). Furthermore, it was only in this group that titres ⩾ 1024 were significantly more common than in the control group ($\chi^2 = 11{\cdot}79$, $P < 0{\cdot}001$). Of the 17 patients in whom serial titres were measured, 3 showed a fourfold or greater rise for a Coxsackie B virus, which in 2 cases rose to ⩾ 1024. In these 2 cases, however, there was no history of a febrile illness and the symptoms had lasted for 2 and 3 years, respectively, before study.

A titre of ⩾ 1024 was found in 6 of the 12 patients with a history of an acute febrile illness. This was a greater frequency than among the other cardiomyopathy patients but did not reach statistical significance. Serial titres to Coxsackie B viruses were measured in 5 of these patients. None showed a fourfold or greater rise, but in 1 case falling titres from a peak of ⩾ 1024 were shown. Only in those patients with a symptomatic history of duration less than 6 months could a statistically significant association of a titre ⩾ 1024 with a previous febrile illness be demonstrated ($P < 0{\cdot}02$, Table).

Table *Relation between length of history of illness, a previous febrile illness, and high titres (⩾ 1024) to Coxsackie B viruses*

Length of history	*Febrile illness*		*No febrile illness*	
	Total	*High titre*	*Total*	*High titre*
All patients	12	6 (50%)	38	9 (24%)
< 1 year	7	5 (71%)	17	6 (35%)
< 6 months*	5	4 (80%)	10	1 (10%)

*P < 0·02, Fisher exact test.

Among the 8 patients who admitted to more than social drinking, a titre of ⩾ 1024 was found in 1 and a titre of 512 in a further 1. There was no tendency for these patients to have a longer history of symptoms before study than the other patients with cardiomyopathy.

Antibody titres to the organisms responsible for influenza, measles, psittacosis, and Q fever were also measured using standard techniques. They were infrequently raised and were similar in cardiomyopathy and control patients. In no patient or control was hepatitis B antigen detected.

CARDIAC BIOPSIES

There was no histological evidence of myocarditis or necrosis in the endomyocardial biopsy specimens. No virus was cultured, and electron microscopy of ultrathin sections disclosed no structures identifiable as viral particles.

HLA ANTIGENS

The distribution of HLA antigens determined in 20 cardiomyopathy patients did not differ from that found in a local normal population. Antigens AW19 (A29 and AW30/31) occurred in 4 patients; none of whom had a high titre to a Coxsackie B virus.

Discussion

Reliable diagnosis of cardiac infection by Coxsackie B viruses is often difficult even during an acute illness. It depends largely on showing the presence of virus within the heart or pericardium and simultaneously rising serological titres (Lerner and Wilson, 1973). Neither electron microscopy nor isolation techniques gave any evidence of Coxsackie B virus in our myocardial biopsies. This is consistent with previous immunofluorescence studies both of human biopsies (Kawai, 1971) and of mouse myocardium after Coxsackie infection (Wong *et al.*, 1977a). It contrasts with the high incidence of positive immunofluorescent staining in a series of routine necropsies by Burch *et al.* (1967), whose findings have never been independently confirmed.

According to accepted criteria (Lerner and Wilson 1973) a single high serum antibody titre is an investigation with a low order association for establishing a viral aetiology. The ubiquity of Coxsackie B viruses and the tendency for titres to be boosted heterotypically make interpretation difficult. However, titres of 512 and over are thought to be strongly suggestive of recent infection (Grist and Bell, 1974). The significantly higher titres found in this study in the patients with congestive cardiomyopathy confirm a previous, smaller study (Kawai, 1971). There is no reason to believe that Coxsackie B antibodies are stimulated by the presence of cardiac failure. However, to investigate this possible artefact, we divided the control patients into two groups according to whether they were taking regular diuretics. There was no tendency for controls with cardiac failure by this definition to have higher titres to the Coxsackie B viruses.

The relation to recent infection is supported by the finding that high titres are significantly more common than in the controls only in patients giving a short clinical history. This also explains the failure to show raised viral antibodies in previous studies of patients with congestive cardiomyopathy, in whom the clinical history was usually longer than one year before study (Sanders, 1963; Fletcher *et al.*, 1968). Accurate definition of the length of history in congestive cardiomyopathy is difficult. Clinical presentation is commonly at the onset of cardiac failure, which may, as in one of our cases, occur several months after subclinical cardiomegaly has already developed. However, it is likely that grouping of a large number of patients by length of clinical history will separate with some accuracy those with a more prolonged disease.

It might be argued that some of the cases with a short clinical history before study should be considered as myocarditis rather than chronic cardiomyopathy. The relation of high titres to the history of a previous febrile illness supports such a contention. This is not, however, strong evidence since it is only significant for the small number of patients in whom the febrile illness occurred within 6 months of the virological study. Chronic congestive cardiomyopathy was diagnosed in all cases, since there was evidence of persistent cardiac failure in the absence of any clinical features of recurrent or relapsing myopericarditis. Furthermore, endomyocardial biopsies of 18 of the patients, including 3 of the 5 with a recent febrile illness, did not show any features of myocarditis.

The evidence that Coxsackie B viruses are involved in initiating congestive cardiomyopathy in man remains circumstantial; but our findings encourage research into the mechanisms of myocardial cell damage by these viruses. There is no evidence that serum antibodies to Coxsackie B viruses are themselves of pathogenetic importance. Recent experiments in mice (Wong *et al.*, 1977b) have shown that after Coxsackie B_3 infection cytotoxic 'T' lymphocytes can be raised which will damage myocardial cells *in vitro*. As yet, there is no direct evidence that these cells can mediate chronic myocardial damage.

The major histocompatibility complex in mice has been associated with sensitivity to viral infections (*British Medical Journal*, 1976). In man, the neurotropism of poliomyelitis appears to be partly dependent on the presence of HLA antigens A3 or A7 (Morris and Pietsch, 1973). Antigens of the AW19 group have been associated with 'chronic rheumatic heart disease' in the absence of a history of rheumatic fever; and it has been suggested that these foci might act as conditioning factors converting a viral myocarditis into a severe pancarditis (Ward *et al.*, 1976). We have found no specific focus to be associated with congestive cardiomyopathy and cannot therefore give support to this theory.

The aetiological significance of Coxsackie B group viruses in human congestive cardiomyopathy may lie in their role as a trigger for immunologically mediated damage to the myocardium. Predisposing or circumstantial factors at the time of infection may act synergistically in the initiation and continuation of the pathological changes. There is good evidence in mice that factors such as exercise, age, steroids, and malnutrition conspicuously affect the severity of myocarditis after Coxsackie B infection. The suggestion that some specific HLA foci might act as such a predisposing factor in man is not substantiated in this study. It is possible, however, that there are changes in cell-mediated immune responsiveness in patients with congestive cardiomyopathy and that investigation of this aspect may shed further light on the aetiology of this disease.

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Heart size and function in acromegaly

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SUMMARY Cardiac size and function was studied in 23 acromegalic patients using echocardiography and systolic time interval measurements. Thirteen patients (56%) had increased left ventricular mass, and in the 20 treated patients this correlated well with the mean of the recent basal growth hormone levels. It is suggested that myocardial hypertrophy may regress in proportion to the degree of control of growth hormone levels. The ejection fraction was normal in all patients except one, and increased left ventricular mass was not associated with detectable impairment of left ventricular performance. Thus, most acromegalic hearts function normally even when their mass is considerably increased, though the long-term effects of this are unknown. Echocardiography will be valuable in the serial monitoring of the cardiac effects of acromegaly.

Cardiac enlargement has been known to be a feature of acromegaly since the end of the last century (Huchard, 1895), and an increase in overall cardiac mass, occasionally to an extreme degree, is typically found at necropsy (Courville and Mason, 1938; Hejtmancik *et al.*, 1951). Heart failure is an uncommon but well-recognised complication, and may occur even in the absence of associated hypertension or ischaemic heart disease (Courville and Mason, 1938; Pepine and Aloia, 1970). It might be expected that the increase in cardiac mass leads to impaired performance, but there is little documented evidence to support this, nor is it established whether the myocardial hypertrophy is reversible after treatment of acromegaly. We have, therefore, studied a group of acromegalic patients, using echocardiographic recordings and systolic time interval data to estimate both left ventricular mass and performance, in order to investigate the relation between these two indices, and to consider the possible effects of treatment on left ventricular mass.

Patients (see Table 1)

Studies were made on 23 patients in whom a diagnosis of acromegaly had been made from the clinical features and demonstration of a resting, fasting growth hormone (GH) level exceeding 10 mU/l which was not suppressed by a 50 g oral glucose load. There were 12 men and 11 women, with ages ranging from 24 to 80 years (mean age 46 years). The estimated duration of the disease ranged from 1 to 30 years. Thirteen patients had been treated by hypophysectomy (with or without external radiotherapy), 7 patients had been treated conservatively by external radiotherapy only, and 3 patients were untreated. Nine patients were receiving hydrocortisone and thyroxine replacement therapy. Eighteen patients had normal GH levels at the time of the study, and in 15 of these the levels had remained within the normal range for at least 1 year. Four patients (cases 5, 8, 10, and 23) had moderate to severe hypertension (blood pressure $\geqslant$ 160/110 mmHg), and 4 patients (cases 19, 20, 21, and 22) had mild hypertension (130/95 to 150/100 mmHg). Case 7 had coexisting Addison's disease and had been receiving treatment with cortisol and fludrocortisone for 12 years. Case 20 had overt diabetes, and had a myocardial infarction 1 year before the study. None of the other patients had a history suggestive of ischaemic heart disease, and none had the clinical symptoms or signs of cardiac failure.

Methods

Each patient attended the outpatient clinic in a fasting state. A standard 12-lead electrocardiogram was performed and a chest radiograph was taken. Blood was taken after the patient had rested for 30 minutes, and the growth hormone concentration was measured by double antibody radioimmunoassay (Hartog and Wright, 1969), using a W.H.O. standard.

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Table 1 *Clinical details of acromegalic patients*

Case no.	*Age (y)*	*Sex*	*Blood pressure (mmHg)*	*Estimated duration of disease (y)*	*Time since treatment (y)*	*Growth hormone concentration*		
						Initial	*Current (mU/l)*	*Mean recent**
1	24	F	130/80	8	5	—	5·2	3·0
2	24	F	140/80	11	6	300	7·0	8·0
3	27	F	120/70	2	1	20	4·8	5·0
4	28	F	120/80	9	8	340	2·4	2·0
5	48	F	160/115	13	8	76	9·0	13
6	49	F	140/90	4	3	114	4·8	7·0
7	53	F	120/80	1	–	176	176	—
8	57	F	220/110	16	1	125	1·0	1·5
9	58	F	140/90	7	2	24	5·6	22
10	59	F	140/110	9	6	11	1·8	4·0
11	67	F	135/90	10	7	60	5·5	8·0
12	27	M	120/80	10	6	26	1·2	1·0
13	28	M	140/80	14	–	420	420	—
14	36	M	140/90	4	2	200	2·2	6·0
15	37	M	120/80	10	9	44	4·5	7·0
16	41	M	120/80	2	1	60	1·9	2·0
17	46	M	120/80	12	3	100	1·3	21
18	49	M	120/85	10	3	37	3·1	2·0
19	51	M	135/100	12	3	12	2·2	7·0
20	55	M	130/95	8	5	290	18	17
21	56	M	150/100	30	–	30	30	—
22	57	M	150/95	27	5	61	5·2	6·0
23	80	M	190/110	6	4	34	14	21

*Mean recent = the mean of the basal growth hormone estimations performed during the 12 months before the study (usually 3 samples).

ECHOCARDIOGRAPHIC RECORDINGS

These were made using an Ekoline 20 ultrasonoscope and a 2·25 MHz focused transducer, the output being displayed through a Cambridge multichannel recorder together with a standard electrocardiographic lead, and recorded on photographic paper at 50 mm/s. The transducer was adjusted to obtain optimal recordings of both the interventricular septum and left ventricular posterior wall.

Analysis of the echocardiograms was carried out by one of us (M.J.B.) without knowledge of the patients' clinical and laboratory findings. The following measurements were made from the anterior edges of the appropriate echoes, taking the mean values of 5 cardiac cycles:

(1) The left ventricular internal diameter, both at end-diastole (LVD) and at end-systole (LVS).

(2) The interventricular septal thickness (ST) at end-diastole.

(3) The left posterior wall thickness (PWT) (the distance between the endocardial and epicardial echoes at end-diastole). Measurement from the anterior edges of these echoes gives a smaller normal range than that usually quoted (Feigenbaum, 1976) but is theoretically more valid (Roelandt, 1977) and has produced a range of left ventricular mass in 20 normal subjects of 80 to 200 g (mean 140 g); this corresponds well to that of 91 to 203 g (mean 135 g) reported from necropsy examination of normal hearts (Reiner *et al.*, 1959).

The following calculations were made (Feigenbaum, 1976):

(1) Ejection fraction of the left ventricle (EF)

$$= \frac{\mathrm{LVD}^3 - \mathrm{LVS}^3}{\mathrm{LVD}^3}$$

(2) Left ventricular mass (LVM)

$$= [(\mathrm{LVD} + \mathrm{ST} + \mathrm{PWT})^3 - \mathrm{LVD}^3] \times 1{\cdot}05$$

(where 1·05 = specific gravity of cardiac muscle).

SYSTOLIC TIME INTERVAL MEASUREMENTS

These were made from simultaneous recordings of high frequency phonocardiograms, carotid pulse (using a hand-held funnel pick-up, air-coupled to a crystal transducer), and the standard electrocardiographic lead which showed the earliest onset of the QRS complex, using the Cambridge recorder on photographic paper at 200 mm/s. Values for the pre-ejection period (PEP), left ventricular ejection time (LVET), and hence the PEP/LVET ratio were derived according to the method described by Weissler and Garrard (1971), again without knowledge of the clinical details of the patient concerned.

Results (see Table 2)

LEFT VENTRICULAR MASS (LVM)

Thirteen patients (56%) showed increased left ventricular mass, which exceeded 300 g in 5 patients, and in 3 of these (cases 9, 13, and 17) was more than 400 g. In general the left ventricular

Table 2 *Echocardiographic and systolic time interval measurements and calculations*

Case no.	*Posterior wall thickness (cm)*	*Interventricular septal thickness (cm)*	*Left ventricular mass (g)*	*Ejection fraction*	*PEP/LVET ratio*
1	0·8	1·0	249	0·75	0·31
2	0·9	0·9	227	0·70	0·38
3	0·85	0·8	134	0·66	0·41
4	0·8	0·75	173	0·71	0·41
5	1·2	1·3	221	0·78	0·39
6	1·0	1·25	288	0·70	0·41
7	0·6	0·50	158	0·41	0·80
8	1·0	0·95	138	0·72	0·33
9	1·5	2·0	583	0·66	0·38
10	0·8	1·5	246	0·76	0·31
11	0·85	0·9	173	0·66	0·35
12	1·0	0·7	134	0·69	0·38
13	1·5	1·4	788	0·69	0·41
14	1·0	0·95	277	0·73	0·37
15	0·7	0·8	189	0·70	0·37
16	0·75	0·7	116	0·68	0·42
17	1·2	1·6	489	0·70	0·33
18	1·0	1·2	213	0·71	0·42
19	0·85	0·9	174	0·69	0·39
20	0·95	1·7	321	0·70	0·63
21	0·9	0·8	136	0·84	0·39
22	1·05	1·3	272	0·66	0·52
23	1·05	1·0	372	0·68	0·53
Normal subjects					
Mean	0·7*	0·8*	140*	0·75*	†0·35
SD	0·1	0·1	30	0·07	0·04
Range	0·5-0·9	0·6-1·0	80-200	0·61-0·89	0·27-0·43

*Values obtained from 20 normal subjects (10 men and 10 women) aged 24 to 54 years (mean 39 years).
Normal values published by Weissler and Garrard (1971).

hypertrophy was concentric in nature, but in 4 patients (cases 9, 10, 17, and 20) the interventricular septum was disproportionately thick.

EJECTION FRACTION

This was within normal limits in all patients except one (case 7).

SYSTOLIC TIME INTERVAL MEASUREMENTS

The PEP/LVET ratio was abnormally high in 4 patients (cases 7, 20, 22, and 23).

ELECTROCARDIOGRAMS

These were within normal limits, except in case 20 who had evidence of a previous myocardial infarction, and cases 19 and 23 who had abnormally flattened T waves in leads I, aVL, and V4-6.

RADIOGRAPHS OF CHEST

The cardiothoracic ratio exceeded 0·5 in 2 patients (cases 5 and 9), but in general the correlation between heart size shown radiologically and that measured by echocardiography was poor.

Discussion

Myocardial hypertrophy, indicated by an increased left ventricular mass, was present in 13 (56%) out of 23 patients with acromegaly of widely varying severity. There was no correlation between increase in left ventricular mass and either the estimated duration of the disease or the GH levels before treatment. Similarly, there was no correlation between increase in left ventricular mass and the presence or severity of hypertension; indeed the 3 patients with the greatest left ventricular mass (cases 9, 13, and 17) were normotensive.

However, the persistence of high GH levels after treatment appeared to be important. Thus, we found a close relation between the left ventricular mass and the mean value of the basal GH levels during the year before the study in the 20 treated patients (Fig.). The left ventricular mass was normal or only moderately raised in the 15 patients whose GH levels had been well controlled for at least 1 year, whereas it was clearly greater in 4 of the 5 patients in whom the treatment had been unsuccessful, or in whom reduction of GH levels was very recent; only 1 of these 4 patients had associated hypertension. Though echocardiography was not performed before treatment, this relation suggests that the myocardial hypertrophy of acromegaly may regress after treatment in proportion to the degree of control of GH levels. However, serial studies on these patients are needed to confirm this.

One of the 3 untreated patients (case 13) had very

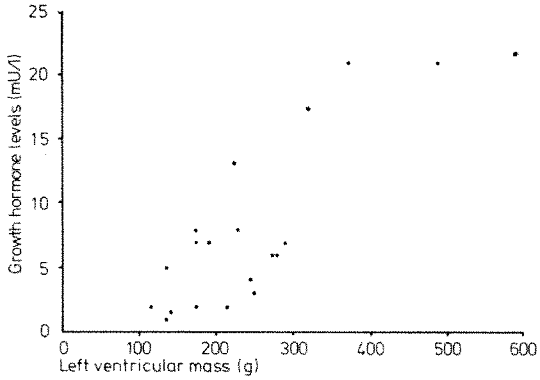

Fig. *The relation between left ventricular mass and mean recent growth hormone levels in treated acromegalic patients.*

high GH levels and a correspondingly high left ventricular mass, but in the other 2 untreated patients (cases 7 and 21) the left ventricular mass was normal, despite raised GH levels. However, in case 7 the acromegaly was of recent onset, and moreover this patient also had Addison's disease. The other patient (case 21) was unusual in that the clinical appearances of acromegaly had remained unchanged for many years.

Our finding that the majority of the patients with hypertrophy manifested a concentric increase in wall thickness and that only a small number of patients appeared to have a disproportionately thick septum accords with the experience of others (Bodem *et al.*, 1976; Savage *et al.*, 1976). The suggestion in a recent report (Hearne *et al.*, 1975) that this latter feature occurs in almost all acromegalics, and is thus a diagnostic feature, was not substantiated; indeed it is now recognised that a minority of patients with left ventricular hypertrophy from any cause (such as aortic stenosis) may have disproportionate septal thickening (Maron *et al.*, 1977) and it appears that acromegalic hearts show the same general pattern.

The use of the left ventricular ejection fraction to evaluate myocardial performance is well established, and a good correlation exists between the values of ejection fraction derived from echocardiographic measurements and those obtained by angiography (Feigenbaum *et al.*, 1972; Murray *et al.*, 1972), provided that there is no segmental wall motion abnormality (Feigenbaum, 1976). The ratio of pre-ejection period (PEP) to left ventricular ejection time (LVET) has been shown to be increased in subjects with heart failure (Weissler *et al.*, 1968) and has also been used as an index of left ventricular performance. Only 1 patient (case 7) in our series of 23 acromegalic subjects was found to have an abnormally small ejection fraction, and this patient also had the highest PEP/LVET ratio; she was atypical in that her acromegaly was superimposed on long-standing Addison's disease but, since she had been receiving apparently adequate adrenocortical hormone replacement therapy for many years, the contribution of this additional factor was difficult to assess. In the other 22 patients the ejection fraction was normal. Three of these other patients had an abnormally high PEP/LVET ratio (in each case resulting from a prolonged pre-ejection period) but in 2 this can be attributed to other factors, namely the previous myocardial infarction of case 20 (Weissler and Garrard, 1971), and the advanced age of case 23 (Harrison *et al.*, 1964). The explanation in case 22 is obscure, but the reliability of systolic time interval criteria in the individual subject has been questioned since falsely positive and negative values are not uncommon (Braunwald *et al.*, 1976), and there is now considerable evidence favouring ejection fraction as the best overall index of basal left ventricular function (Braunwald *et al.*, 1976). Thus we found convincing evidence of subclinical impairment of myocardial performance in only 1 patient (case 7); further, there was no correlation between the left ventricular mass and either the ejection fraction or the PEP/LVET ratio.

It does not, therefore, seem that increasing myocardial hypertrophy leads to impaired function, and indeed most acromegalic hearts appear to function well, regardless of size. This is in agreement with other reports (Bodem *et al.*, 1976; Martins *et al.*, 1977). Our study does not support the findings of a report on 10 acromegalic patients, in which a high incidence of subclinical muscle disease was suggested on the basis of systolic time interval measurements alone (Jonas *et al.*, 1975). However, the PEP/LVET ratio was strikingly abnormal in only 2 patients in the above report, 1 of whom had previously had a myocardial infarction; in the other patients the abnormal ratios were largely the result of a shortened left ventricular ejection time with a normal pre-ejection period, which is not the pattern that theoretical considerations would predict in subclinical myocardial disease. The low incidence of subclinical myocardial impairment in our acromegalic patients contrasts with the high prevalence of overt cardiac failure described in earlier reports (Courville and Mason, 1938; Hejtmancik *et al.*, 1951). It is possible that this represents a true fall in the incidence of myocardial dysfunction, related in part to earlier and more effective definitive treatment.

In conclusion, we found that considerable myocardial hypertrophy in treated patients was only present when control of growth hormone levels was inadequate, suggesting that the former may be at least partially reversible after effective treatment. There was no evident correlation between myocardial hypertrophy and performance, and indeed the latter was normal in all patients except one. Nevertheless, the long-term functional effects of the hypertrophy, persisting over decades, remain unclear. The serial use of echocardiography in individual patients promises to be of importance in assessing the effect of treatment in preventing potentially serious alterations of heart size and function in acromegaly.

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Long-term follow-up in primary pulmonary hypertension

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SUMMARY Two patients with severe primary pulmonary hypertension, who are alive 38 and 27 years after the onset of the disease, were closely followed by the authors for 24 years. No previous report of such a long course has been found. Despite pulmonary artery pressures at systemic level, effort syncope disappeared and there were long intervals without symptoms during which the 2 patients were able to take part in physical activity with minimal discomfort. Severe primary pulmonary hypertension should not always be considered a malignant disease.

In most cases of primary pulmonary hypertension the onset of symptoms is followed by death within a period of a few months up to 3 years (Wood, 1956). Effort syncope and uncontrollable acute or chronic heart failure are the most common causes of death (Fowler *et al.*, 1966; Degeorges *et al.*, 1970). In addition death may occur during, or shortly after, cardiac catheterisation (Schafer *et al.*, 1956), or during very simple procedures such as the determination of the circulation time (Cutler *et al.*, 1954). No effective treatment is yet available, and many therapeutic measures may even be dangerous (Inkley *et al.*, 1955). As a consequence of all these features primary pulmonary hypertension has been considered a malignant disease. However, a careful review of available publications reveals several cases with a survival of 10 to 20 years (McCallum, 1931; Wood, 1956; Nielsen and Fabricius, 1961; Sleeper *et al.*, 1962; Melmon and Braunwald, 1963; Fowler *et al.*, 1966; Charters and Baker, 1970; Degeorges *et al.*, 1970). Patients with an unusually long history, 20 to 29 years, were reported by Wagenvoort and Wagenvoort (1970). Recently, Trell (1973) described 2 patients whose disease lasted 27 and 40 years respectively, though both had only moderate degrees of pulmonary hypertension for most of the duration of their illnesses.

From March 1953 to the present, 24 cases of severe primary pulmonary hypertension have been studied by the authors at the Hospital de Clínicas of Buenos Aires. Two of them, who are alive 38 and 27 years after the onset of the disease, were closely followed up for 24 years. Both patients were included (cases 1 and 2) in a previous early series (Perosio *et al.*, 1960). A description of the chief features of these unusual cases is the purpose of this report.

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Patients

CASE 1

A 29-year-old woman was admitted to the Hospital de Clínicas in November 1954 because of fatigue and dyspnoea on exertion experienced during the past 14 years; since 1950 she had had 3 episodes of effort syncope. In addition, at the age of 17, symptoms of typical rheumatoid arthritis developed, and the patient was told that she had rheumatic valvular heart disease. During the previous 12 years she had been admitted several times to different hospitals with the same diagnoses. She gave no history suggestive of thromboembolism and there was no family history of heart disease.

Physical examination disclosed slight cyanosis of the lips and cheeks. Pronounced deformities of the rheumatoid arthritis type were present. The blood pressure was 115/75 mmHg. The jugular venous pulse revealed prominent *a* waves. The cardiac impulse was powerful, sustained, and was maximal at the lower left sternal border. On auscultation an ejection click could be heard in the pulmonary area. A fourth heart sound was present. The second heart sound was closely split with a

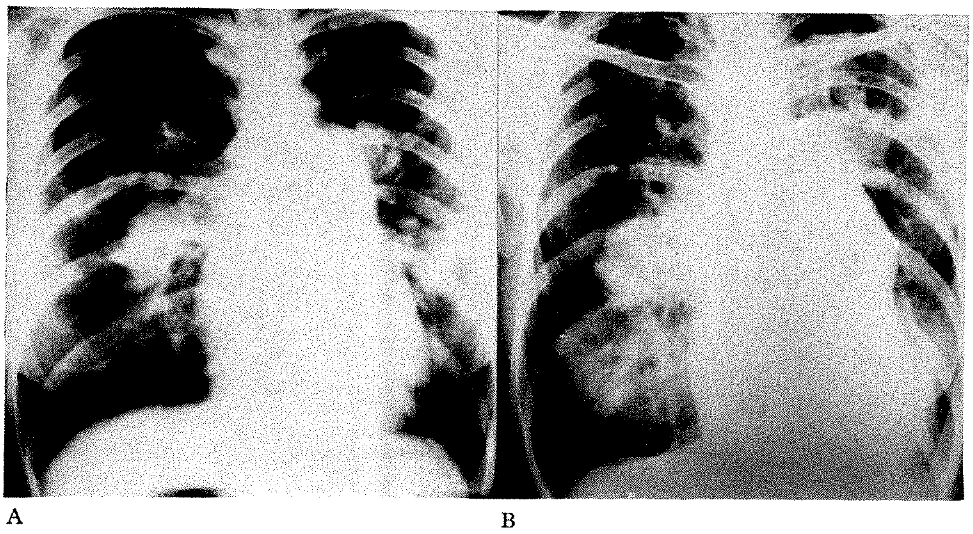

Fig. 1 *Case 1.* X-*ray pictures of November 1954 (A), and March 1978 (B).*

loud pulmonary component at the second left interspace, followed by an immediate decrescendo diastolic murmur of the Graham Steell type.

The chest *x*-ray film showed right ventricular enlargement, prominent main pulmonary segment, considerable dilatation of the two main branches of the pulmonary artery, and diminished peripheral pulmonary vascularity (Fig. 1A). The respiratory function tests and the values for alveolar Po_2 and Pco_2 were normal.

The electrocardiogram showed a mean QRS frontal axis of + 120°, tall R waves in right and mid-praecordial leads with a qR pattern in V1, and negative T waves in II, III, aVF, and in all the praecordial leads (Fig. 2A). The vectorcardiogram (Grishman's cube system) showed clockwise inscription of the QRS loop in both the frontal and horizontal planes. The initial forces were directed to the left, and the body of the QRS loop was displaced anteriorly and rightward. Discordant T loops were recorded (Fig. 3A).

A haemodynamic study showed the following: (1) there was no evidence of a left-to-right shunt, and the systemic arterial oxygen saturation was normal; (2) the pulmonary arterial and right ventricular pressures were at systemic level; (3) pulmonary artery wedge pressure was normal; and (4) pulmonary resistance was much increased (Table). Right angiograms showed gross dilatation of the pulmonary trunk and its main branches, with lack of arborisation of the pulmonary vascular tree (Fig. 4). A few minutes after the cardiac catheterisation, the patient abruptly developed typical pulmonary oedema. The treatment was effective, but 15 minutes later the patient's blood pressure dropped precipitously and other signs of circulatory collapse followed. Plasma (500 ml) and an infusion of 4 mg/1000 ml of noradrenalin were administered. Six hours later the patient improved. She remained well and was discharged from hospital. No special treatment was instituted, except a sodium-free diet and digoxin 0·25 mg daily.

From December 1954 to July 1961 the patient experienced 3 episodes of loss of consciousness during heavy exercise. But for the next 5 years she remained asymptomatic. Digoxin was then discontinued.

In August 1966, she presented with 2 haemoptyses with symptoms of right-sided heart failure. There were no symptoms to suggest venous thrombosis or pulmonary embolism. Two weeks later she improved steadily and from September 1966 to July 1969 was asymptomatic. Treatment was discontinued in November 1969.

In June 1971, the patient developed bacterial pneumonia and symptoms of right-sided heart failure recurred. The electrocardiogram was unchanged from the earlier admission. Chest *x*-ray film showed a typical pneumonic shadow in the upper left lung field. Treatment with penicillin, streptomycin, digoxin, frusemide, and oxygen was effective.

An echocardiogram was first recorded in June 1973 and showed right ventricular enlargement with normal left atrial size. The mitral valve was normal (Fig. 5).

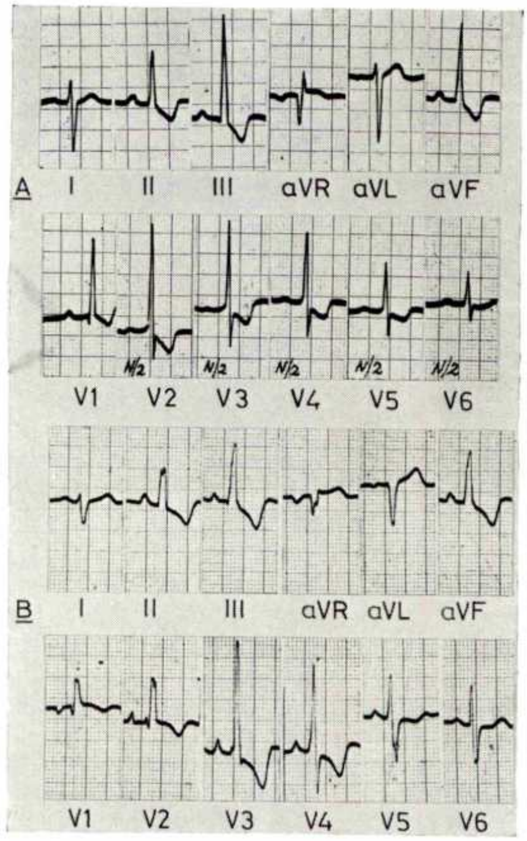

Fig. 2 *Case 1. Electrocardiograms recorded in November 1954 (A), and in March 1978 (B). Calibration, 1 cm = 1 mV, except in V2 to V6 of the tracing A in which 0·5 cm = 1 mV.*

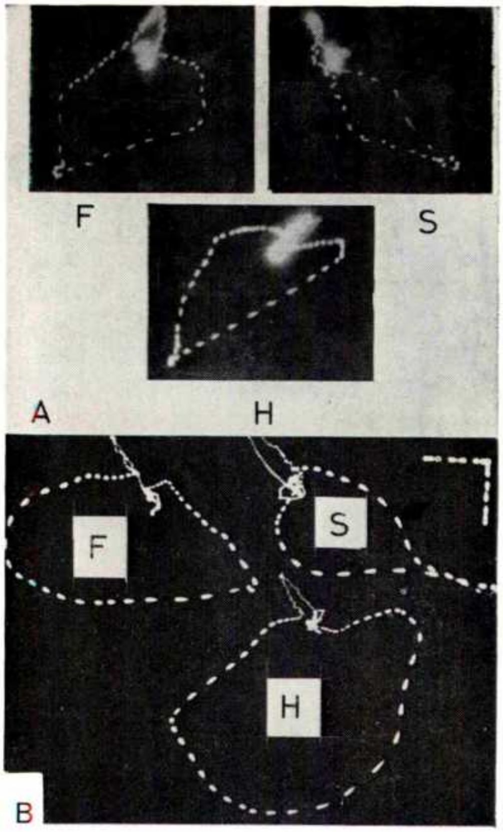

Fig. 3 *Case 1. Vectorcardiograms recorded in November 1954 with the Grishman's cube system (A), and in March 1978 with the Frank system (B). Calibration signal, 0·5 mV.*

From 1973 to the present (June 1978) the patient has remained well and she can do all her house work without discomfort. On examination in March 1978 the physical findings were substantially the same as those in 1954 (Fig. 6). The electrocardiogram showed the following changes: (1) a greater duration of the QRS complexes, (2) signs of right atrial hypertrophy, and (3) positive T waves in left praecordial leads (Fig. 2B). The vectorcardiogram recorded with the Frank system revealed a rightward shift of the T loop in both the horizontal and frontal planes (Fig. 3B). The chest *x*-ray film showed an increase in the size of the cardiovascular shadow, and increased prominence of the pulmonary trunk and dilatation of its main branches (Fig. 1B).

Table *Haemodynamic data*

Case no.	*Right atrium*	*Right ventricle*	*Pulmonary artery*	*Pulmonary artery wedge*	*Brachial artery*	*Total pulmonary resistance (dynes cm s^{-5})*	*Cardiac index (l/min per m^2)*
1 Pressures (mmHg) S/D-M	5/3-4	94/3	94/60-75	12/1-4	110/75-90	1517	2·89
O_2 saturation (%)	66·5	67·2	66·1	98·1	96·7		
2 Pressures (mmHg) S/D-M	5/2-3	110/2	110/60-75	6/1-3	95/65-78	1411	3·14
O_2 saturation	63·4	62·3	63·5	97·9	94·7		

S/D-M, systolic/diastolic-mean.

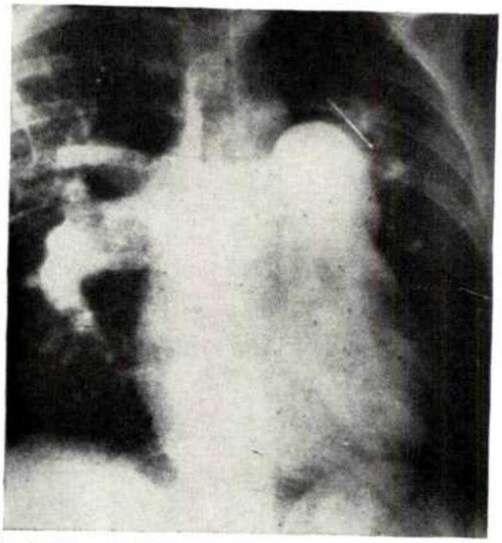

Fig. 4 *Case 1. Right angiogram obtained in November 1954 showing gross dilatation of the pulmonary trunk and its main branches with lack of arborisation of the pulmonary vascular tree.*

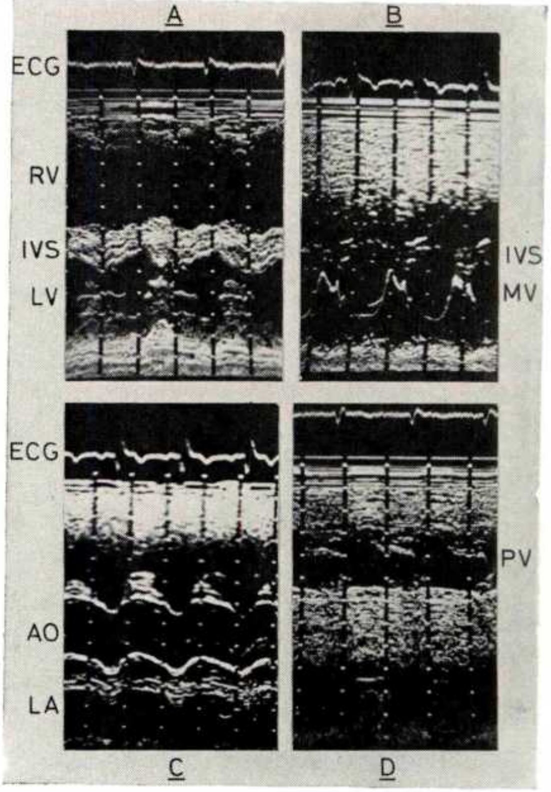

Fig. 5 *Case 1. Echocardiogram recorded in June 1973 showing dilatation of the right ventricle (A), normal mitral valve (B), normal left atrial size (C), absence of the* a *wave and mid-systolic closure of the pulmonary valve (D). IVS, interventricular septum; RV, right ventricle; LV, left ventricle; MV, mitral valve; AO, aorta; LA, left atrium; PV, pulmonary valve.*

CASE 2

A 6-year-old boy was first seen in July 1954 because of fatigue, dyspnoea on exertion, and effort syncope. These symptoms had begun by the time he was 3 years of age. During the previous year he had had 7 syncopal attacks. Slight cyanosis on exertion was noted by his mother.

On examination the blood pressure was 100/70 mmHg. The cardiac impulse was prominent under the xiphoid process. On auscultation a pulmonary ejection click and a closely split second heart sound with a loud pulmonary component were heard in the pulmonary area. In addition a grade 3/6 pansystolic murmur could be heard at the tricuspid area, suggesting functional tricuspid regurgitation.

The chest *x*-ray film showed conspicuous dilatation of the main pulmonary segment, enlargement of the right ventricle, and increased hilar vessels in contrast with decreased peripheral pulmonary vascularity (Fig. 7A). The pulmonary function tests were normal.

The electrocardiogram revealed a mean QRS frontal axis of + 150°, prominent R waves from V4R to V2, and positive T waves in all the praecordial leads (Fig. 8A). The vectorcardiogram showed the typical pattern of right ventricular hypertrophy type A.

The haemodynamic findings were similar to those in case 1 (Table). Right angiograms showed considerable dilatation of the pulmonary artery, with reduced pulmonary vascularity and no evidence of intra or extracardiac shunts.

During the first 4 years of follow-up, tolazoline, aminophylline, and digoxin were administered. In spite of this treatment he experienced several episodes of effort syncope. Nevertheless, he looked healthy when examined in 1958. The auscultatory, radiological, and electrocardiographic findings were similar to those recorded in 1954.

From 1958 to 1963 the patient improved. He experienced slight dyspnoea on exertion but sometimes he could carry out physical activities without breathlessness. On examination in June 1964, slight venous congestion with prominent *a* waves could be seen in the neck. At this time a grade 3/6 diastolic murmur was found in the pulmonary area and along the left sternal border.

Since 1964 there have been no further episodes

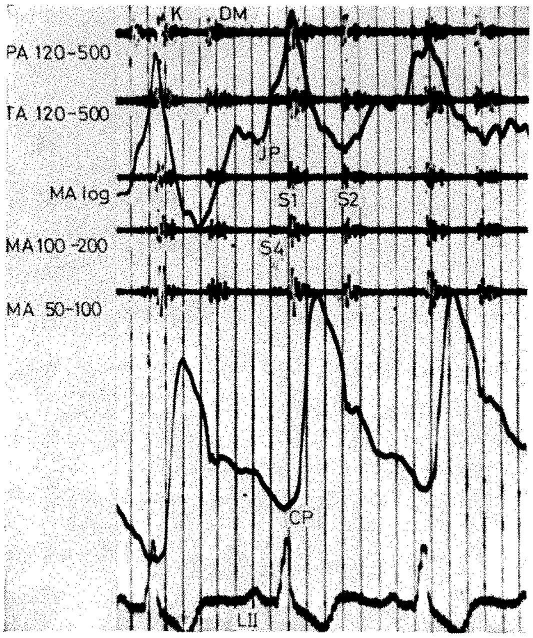

Fig. 6 *Case 1. Logarithmic (Log), and filtered (120-500 Hz) phonocardiograms, recorded simultaneously with the jugular pulse (JP), the carotid pulse (CP), and the electrocardiogram (lead II), showing a fourth heart sound (S4), a pulmonary ejection click (K), the splitting of the second heart sound (S2) with a loud pulmonary component, and the diastolic murmur of the Graham Steell type (DM). Note the giant* a *waves in the jugular venous pulse. Paper speed, 50 mm/s. PA, pulmonary area; TA, tricuspid area; MA, mitral area.*

of effort syncope. Throughout the next 10 years there was an alternating course of asymptomatic periods and times when symptoms of moderate right-sided heart failure and low pulmonary output were present. The causes of these changes in the clinical status of the patient were not evident: sometimes it was thought that influenza or bronchitis was responsible.

A phonocardiogram recorded in September 1974 revealed no changes in the auscultatory findings. The echocardiogram showed similar features to those in case 1.

During the last 3 years the patient has remained well. Physical findings are unchanged. The electrocardiogram shows an increase in P wave voltage. Conversely the R waves in the right praecordial leads are smaller than those observed in 1954 (Fig. 8B). The chest *x*-ray film shows reduced cardiothoracic ratio, though there has been an increase in the dilatation of the main pulmonary segment with diminished peripheral pulmonary vascularity (Fig. 7B).

Discussion

Recently an effort was made by the World Health Organization (Hatano and Strasser, 1975) to clarify the aetiology and pathology of primary pulmonary hypertension. At this meeting it was stated that three pathological entities could be found. These entities are (1) plexogenic pulmonary arteriopathy, (2) recurrent pulmonary thromboembolism, and (3) pulmonary veno-occlusive disease. The prognosis seems to be different in each of these three types. The pulmonary veno-occlusive form has the more severe course, and life expectancy is usually between a few months and 2 years. The thromboembolic form has a more benign course and tends to have the longest survival. The plexogenic type lies between these, with a survival up to 3 years. Though our 2 patients have the clinical and radiological presentation of the last type (Hatano and Strasser, 1975), definitive diagnosis is not possible without histological examination obtained either by biopsy or necropsy (Edwards and Edwards, 1977).

From the clinical viewpoint the most sinister prognostic signs in all the reported cases have been recurrent effort syncope and progressive right-sided heart failure (Nielsen and Fabricius, 1961; Fowler *et al.*, 1966; Degeorges *et al.*, 1970; Nadas and Fyler, 1972). The first was present in our 2 patients and especially in case 2. However, after a period of 9 to 12 years this symptom disappeared spontaneously. In the case reported by Charters and Baker (1970), effort syncope also remitted for long intervals, but then recurred and finally the patient died suddenly. Signs of right-sided heart failure were present in the 2 patients, frequently occurring after complicating events; they were easily managed with conventional treatment.

Electrocardiographic evidence of right ventricular hypertrophy is recorded in 100 per cent of cases (Degeorges *et al.*, 1970) and is not useful in assessing prognosis. However, severe right atrial overload and arrhythmias are features which tend to occur in very ill patients and imply a poor prognosis (Delaye *et al.*, 1970). The most recent electrocardiogram in case 1 showed increased QRS duration and increased signs of right atrial overload, though there was little change in the QRS loops in the vectorcardiograms. On the other hand, the recent electrocardiogram in case 2 suggested a lesser degree of right ventricular overload. There was similar regression of electrocardiographic changes in the patient reported by Bourdillon and Oakley

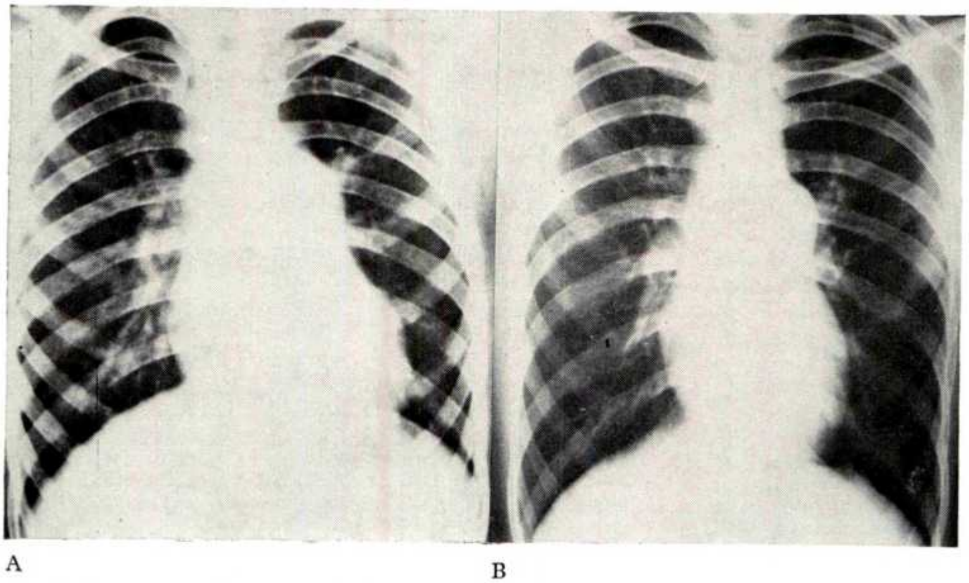

Fig. 7 *Case 2. X-ray films of July 1954 (A), and March 1978 (B).*

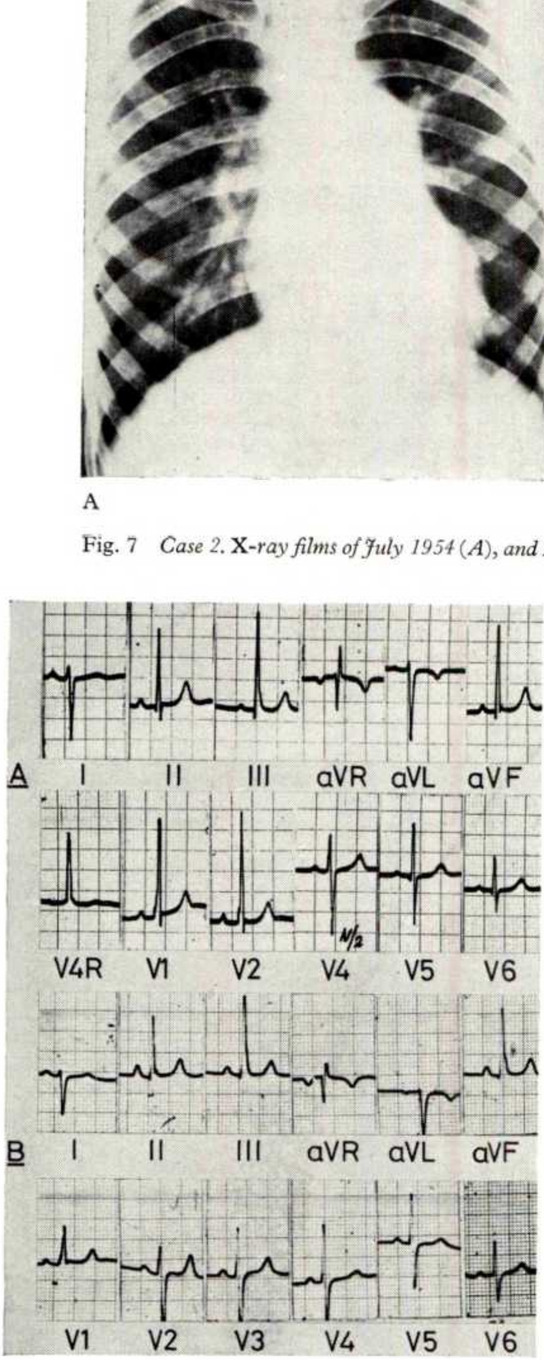

Fig. 8 *Case 2. Electrocardiograms recorded in July 1954 (A), and in March 1978 (B). Calibration 1 cm = 1 mV, except in V4 of the tracing A in which 1 cm = 0·5 mV.*

(1976), in whom there was clinical and radiological improvement with reduction in pulmonary hypertension. In our case 2, however, clinical evidence of right atrial and ventricular overload increased, and the regression of the electrocardiographic right ventricular hypertrophy was probably attributable to a change in the shape of the thorax with growth.

A poor correlation seems to exist between pulmonary arterial pressure or other haemodynamic data and survival (Degeorges *et al.*, 1970). The long survival of our 2 cases supports this concept. However, most patients with severe pulmonary hypertension and low cardiac output follow a relentless downhill course. Few reported cases have had repeated haemodynamic studies (Sleeper *et al.*, 1962; Farrar *et al.*, 1961). Nielsen and Fabricius (1961) were able to repeat cardiac catheterisation in 5 cases: they found that pulmonary pressure increased considerably in 3 but remained unchanged in the other 2. Stabilisation of the haemodynamic abnormalities may explain the relatively benign course in our patients who did not consent to further invasive studies. A similar stable condition over several years in a case with mild pulmonary hypertension was recorded by Trell (1973).

It is interesting to note that in the long course of our 2 patients prolonged intervals without symptoms occurred in spite of discontinuing treatment. Sometimes purulent bronchitis or pneumonia with possible subsequent anoxia seemed to be a likely explanation for relapse, but frequently no cause could be found. Two possibilities were considered.

The first was spontaneous periodic accentuation of the vasomotor tone of the pulmonary vessels of unknown origin, as may be seen in systemic hypertension. The second was a minor pulmonary thromboembolic event or thrombosis *in situ*, findings frequently observed at necropsy in this type of patient.

Further studies are necessary to clarify the importance of these and other causes in the development of the disease. However the long and relatively benign course seen in our patients implies at least that severe primary pulmonary hypertension should not always be considered a malignant disease.

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Clinical electrophysiological effects of propranolol on normal sinus node function

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SUMMARY In 35 patients aged 18 to 69 years (mean 48) with clinical, electrocardiographic, or electrophysiological evidence of normal sinus node function, the effect of intravenous propranolol (0·1 mg/kg) was assessed on 3 indices of sinus node function. The drug significantly prolonged sinus node cycle length (12%), slightly prolonged the corrected sinus node recovery time (15%), and slightly but insignificantly lengthened sinuatrial conduction time. Propranolol may be administered safely in patients with normal sinus node function without the fear of producing severe sinus bradycardia, sinuatrial block, sinuatrial pauses, or prolonged sinus asystole, after spontaneous or stimulation-induced conversion of a tachycardia.

For over a decade, propranolol has been used extensively in the management of patients with arrhythmias (Rowlands *et al.*, 1965; Bath, 1966). Several studies have reported the electrophysiological effects of propranolol in isolated tissue preparations (Davis and Temte, 1968; Pollen *et al.*, 1969), in the intact animal (Priola, 1973), and in man (Seides *et al.*, 1974). Despite a large number of publications, there is little information on the electrophysiological effects of propranolol on the sinus node function in man (Grendahl *et al.*, 1975; Strauss *et al.*, 1976b). Previous studies (Seides *et al.*, 1974) in general analysed the effect of propranolol on only one index of sinus node function, that is the changes in sinus node cycle length or rate. Except for a preliminary report (Chuquimia *et al.*, 1977) from this laboratory, few data are available on the effects of propranolol in patients with normal sinus node function, in particular on the response of the sinus node to overdrive suppression and on sinuatrial conduction time. Recently Strauss *et al.* (1976b) have reported their results on the effect of propranolol in 10 patients with sinus node dysfunction. It is difficult to view their results with a proper perspective without the knowledge of its effects on normal sinus node function.

In view of its extensive clinical use in patients with various types of arrhythmias, especially atrial fibrillation, atrial flutter, or supraventricular tachycardia, which inherently produce overdrive suppression of the sinus node, the necessity to learn the effects of propranolol on various indices of normal sinus node function was realised. The purpose of this study was to analyse the effect of intravenous propranolol on sinus node function in patients with clinical and electrophysiological evidence of normal sinus node function.

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Subjects and methods

Electrophysiological studies were performed in 35 patients. Patients ranged in age from 18 to 69 years (mean 48), with 16 men and 19 women. A complete history and physical examination were recorded. In each patient routine laboratory data, a standard 12 lead electrocardiogram, and a chest *x*-ray film were obtained. The patients included in this study consistently showed resting normal heart rates (> 60/min) on serial electrocardiograms and showed no electrocardiographic (standard electrocardiogram and Holter recordings) or clinical evidence of sinus node dysfunction. In addition, none of the 35 patients had any evidence of sinus node dysfunction during electrophysiological studies which were performed for symptoms of syncope, dizziness, and/or palpitations. The standard electrocardiogram was normal in 11 patients and showed a pattern of bundle-branch block in 9 patients. The remaining

15 patients showed various arrhythmias, that is paroxysmal re-entrant supraventricular tachycardia (7), ventricular arrhythmia (7), and 2° type 1 atrioventricular nodal block (1). In the cases with paroxysmal supraventricular tachcardia, the site of re-entry was either in the atrioventricular node or resulted from bypass tracts. None of the 35 patients showed any evidence of atrial fibrillation or atrial flutter. In 24 patients there was no clinical evidence of associated heart disease, besides the arrhythmia or the bundle-branch block pattern. One patient had arteriosclerotic heart disease and 10 had associated systemic hypertension. At the time of study all cardioactive drugs had been discontinued for an interval exceeding 3 drug half lives. In all patients informed consent was obtained. The patients were studied in the postabsorptive state after premedication with 100 mg pentobarbitone sodium administered intramuscularly half an hour before the study.

Under fluoroscopic control and intracardiac electrographic monitoring, a bipolar electrode catheter, 5 French in size with ring electrodes 10 mm apart was introduced precutaneously from a femoral vein and placed in the His bundle region. His bundle electrograms were recorded as described previously (Narula *et al.*, 1970). A second quadripolar pacing catheter with electrodes 10 mm apart was introduced into the right atrium via an antecubital vein, and positioned so that the proximal electrode pair was located in the region of the sinus node for recording high right atrial electrograms and the distal pair was used for atrial stimulation.

All recordings were made on a multichannel oscilloscopic photographic recorder at paper speeds of 100 mm/s for analyses of AH and HV intervals, and paper speeds of 50 to 100 mm/s were used during studies of sinus node function. Multiple electrocardiographic leads representing the 3 planes of the electrocardiogram were recorded simultaneously with the intracardiac recordings. Atrial stimulation studies were performed at double the diastolic threshold with stimuli 2 ms in duration. Atrioventricular conduction was analysed during sinus rhythm and atrial pacing.

After catheter placement, control observations of spontaneous sinus rhythm were made for a period of 10 minutes. During the last minute of the control period, 10 consecutive sinus cycles were measured to calculate the mean sinus cycle length (mean A_1A_1). Single premature atrial beats were induced during sinus rhythm after every 8th sinus cycle for evaluation of sinuatrial conduction time. The entire sinus cycle was scanned by the placement of premature atrial beats of increasing prematurity in steps of 10 to 20 ms until the atrial refractory period was reached. After the sequence of premature atrial beats, spontaneous sinus rhythm was observed for another period of 2 minutes before analysis of sinus node recovery time. The sinus node recovery time was measured as previously described (Narula *et al.*, 1972) by atrial pacing at 2 different cycle lengths (500 and 430 ms) for a period of 2 minutes at each level. Atrial pacing at cycle lengths shorter than 430 ms was not used, as previous studies Mandel *et al.*, 1971) have reported a decrease in sinus node recovery time with shorter pacing cycle lengths. Immediately after atrial pacing was stopped, 10 spontaneous sinus cycles were recorded and analysed. A rest period of 2 minutes was provided between each atrial pacing rate to permit sinus rhythm to return to control levels. In our study, the sinus cycles usually returned to control levels in less than 1 minute.

After control determinations were completed, propranolol was administered intravenously in a dosage of 0·1 mg/kg bodyweight at a rate of 1 mg/min. Total dose ranged from 5 to 10 mg. This dosage regimen has been reported (Seides *et al.*, 1974) to produce average plasma levels of 13·6 ng/ml for 45 to 60 min after administration of propranolol. Ten minutes after the infusion of the last drop of propranolol, 30 sinus cycles were recorded to obtain the post-propranolol mean sinus cycle length. Thereafter, studies were repeated as in control to measure sinuatrial conduction time and sinus node recovery time. These studies were usually completed in $\leqq$ 30 minutes after the last dose of propranolol was given.

The blood pressure was carefully monitored throughout: the drop in systolic pressure was $\leqq 10$ mmHg in all cases. No complications requiring treatment occurred in any patient either during or after the study. The atrial stimulation studies (regular atrial pacing or premature atrial beats) did not produce any bouts of atrial fibrillation or flutter throughout the study. In none of the cases with a history of supraventricular tachycardia was the measurement of sinus node recovery time or sinuatrial conduction time affected by atrial stimulation studies. Regular atrial pacing at cycle lengths used for sinus node recovery time did not initiate supraventricular tachycardia. During scanning of the sinus cycle by premature atrial beats, supraventricular tachycardia was initiated (3 out of 7) with very early premature atrial beats and not during the zone of sinus node reset used for estimating sinuatrial conduction time. In order to enhance relaxation, patients were studied in a quiet atmosphere and a relatively dark room using as little light as was necessary for the operation of the stimulator and the physiological recorder.

In each patient the intervals between successive atrial depolarisations were measured from the bipolar high right atrial electrogram. During the sequence of premature atrial beats, the following intervals were measured: (1) A_1A_1 which is defined as the interval between the 2 consecutive sinus cycles; (2) A_1A_2 the interval between the atrial electrograms of sinus origin and the premature atrial beat; (3) A_2A_3 (return cycle) the interval between the premature atrial beat and the succeeding sinus beat. The estimated sinuatrial conduction time was calculated by the recently described method of Strauss *et al.* (1976a) based on a mean of A_2A_3 intervals falling in the latter portion of zone II (reset zone). Sinuatrial conduction time = $A_2A_3 - A_1A_1$. The value thus obtained represents the sum total of conduction time into and out of the sinus node.

Sinus node recovery time was measured from the last paced atrial electrogram to the first escape atrial electrogram of sinus origin or the longest post-pacing pause. The corrected sinus node recovery time was obtained by deducting from the sinus recovery time the mean of 10 consecutive spontaneous sinus cycles, recorded immediately preceding each atrial pacing cycle length. The statistical significance of the difference in values of spontaneous sinus node cycle length, corrected sinus node recovery time, and estimated sinuatrial conduction time determined under control and after propranolol were tested using the paired t test.

Results

(1) SINUS CYCLE LENGTH

During control the sinus node cycle length ranged from 559 to 955 ms (mean and SD 766 ± 102) and after propranolol it ranged from 705 to 1090 ms (mean and SD 860 ± 107). After propranolol the sinus node cycle length increased by a range of 6 to 295 ms (mean 94) or by a mean of 12 per cent; this increase was statistically significant ($P < 0{\cdot}005$) (Fig.) None of the patients manifested any electrocardiographic evidence of 2° sinuatrial block or sinuatrial pauses after propranolol administration.

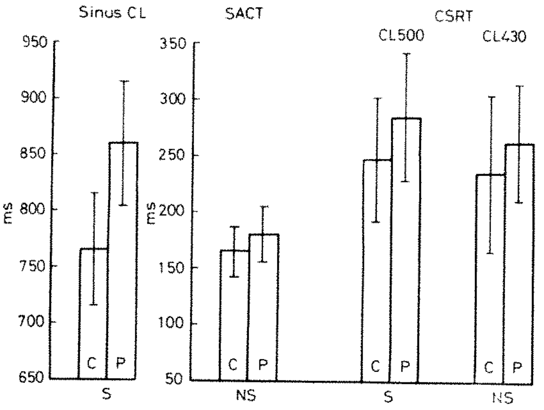

Fig *The effects of propranolol on the 3 indices of sinus node function. NS, statistically not significant.*

(2) SINUATRIAL CONDUCTION TIME

In 2 patients (cases 26 and 32), the sinuatrial conduction time during control was 175 and 118 ms, and it could not be calculated after propranolol as the zone of sinus node reset could not be defined (Table). In the remaining 33 patients, the control sinuatrial conduction time ranged from 70 to 246 ms (mean 166 ± 49) and after propranolol it ranged from 100 to 285 ms (mean 182 ± 49). With propranolol, the sinuatrial conduction time was shortened (range 7 to 92 ms) in 12 and lengthened (range 2 to 110 ms) in 21 patients. The changes in sinuatrial conduction time after propranolol were not statistically significant.

(3) CORRECTED SINUS NODE RECOVERY TIME

On stopping atrial pacing, the first escape sinus node cycle was the longest in all except 4 of the 35 patients, in whom it was noted to be the second or the third sinus node cycle (Table).

The control corrected sinus node recovery time after atrial pacing at cycle length of 500 ms ranged from 83 to 520 ms (mean 247 ± 113) and after propranolol ranged from 90 to 605 ms (mean 284 ± 115) (Fig.). After propranolol, the corrected sinus node recovery time at this atrial pacing rate was unchanged in 2, prolonged in 23 (range 15 to 415 ms, mean = 97), and shortened in 10 patients (range 20 to 175 ms, mean = 93). The control corrected sinus node recovery time after atrial pacing at a cycle length of 430 ms ranged from 10 to 525 ms (mean 235 ± 137) and after propranolol ranged from −55 to 494 ms (mean = 262 ± 106). After propranolol, the corrected sinus node recovery time at this atrial pacing rate was unchanged in 1, lengthened in 23 (range 25 to 276 ms, mean = 102), and shortened in 11 patients (range 5 to 345 ms, mean = 125). After propranolol 17 (49%) of the 35 patients showed a shortening in corrected sinus node recovery time at both atrial pacing cycle lengths. Before beta-blockade, in 8 of these 17 patients, the corrected sinus node recovery time had shortened during control as the atrial pacing rate was increased.

Table *Electrophysiological effect of propranolol on normal sinus node function*

No.	*Age and sex*		*Other electrocardiographic features*	*Sinus cycle length (ms)*		*Sinuatrial conduction time (ms)*		*Corrected sinus node recovery time (ms)*			
								AP CL = 500		*AP CL = 430*	
				Pre	*Post*	*Pre*	*Post*	*Pre*	*Post*	*Pre*	*Post*
1	18	F	Normal PR, QRS, and axis	710	830	150	100	90	90	185	150
2	18	M	Lown Ganong Levine syndrome, supraventricular tachycardia	611	717	119	223	146	243	157	212
3	21	F	WPW and supraventricular tachycardia	559	757	78	123	237	357	235	337
4	23	F	Premature ventricular contractions	870	990	175	200	125	245	85	305
5	26	F	Normal PR, QRS, and axis	900	1005	160	235	520	605	290*	−55
6	29	M	Normal PR, QRS, and axis	892	1020	131	114	265	158*	10	112*
7	30	F	Normal PR, QRS, and axis	682	740	188	190	273	340	234	343
8	36	F	Ventricular tachycardia	950	968	165	172	367	293	525	347
9	38	M	Type 1, 2° atrioventricular block	740	855	210	197	180	215	205	350
10	40	M	Supraventricular tachycardia	915	940	245	215	145	260	180	320
11	42	F	Left bundle-branch block	775	850	205	285	215	380	295	350
12	43	F	WPW and supraventricular tachycardia	700	720	170	120	175	195	130	105
13	45	F	Supraventricular tachycardia	629	718	113	147	95	510	120	310
14	45	F	Left bundle-branch block	764	770	246	265	297	255	114	167
15	46	F	Normal PR, QRS, and axis	787	815	120	230	235	370	182	257
16	50	M	Normal PR, QRS, and axis	680	705	170	245	110	180	60	160
17	52	F	Normal PR, QRS, and axis	728	820	157	120	275	205	150	145
18	52	M	Supraventricular tachycardia	700	850	180	220	380	250	500	210
19	52	F	Ventricular tachycardia	830	880	210	170	280	205	125	290
20	53	M	Right bundle-branch block and left axis deviation	875	955	190	205	430	515	290	360
21	54	M	Left bundle-branch block	700	760	85	170	152	247	125	170
22	55	M	Normal PR, QRS, and axis	898	926	158	130	245	310	400	380
23	55	F	Prolonged QT, premature ventricular contraction	710	790	110	110	140	240	185	250
24	55	M	Ventricular tachycardia	680	790	240	250	400	440	460	410
25	57	F	Right bundle-branch block and left axis deviation	700	750	70	140	300	300	275	360
26	57	F	Ventricular tachycardia	760	960	175	ND	290	380	520	250
27	58	F	Right bundle-branch block and left axis deviation	725	795	230	235	231	324	216	245
28	60	M	Normal PR, QRS, and axis	710	737	180	173	410	325	260	305
29	60	M	Right bundle-branch block and left axis deviation	730	855	100	190	83	105	25	50
30	64	M	Right bundle-branch block and left axis deviation	860	980	165	180	165	145	200	180
31	65	F	Left bundle-branch block	955	1000	155	125	128	264	218	494
32	65	M	Premature ventricular and atrial contractions	927	1090	118	ND	305*	130	320	410
33	68	M	Normal PR, QRS, and axis	730	840	210	195	285	320	470	235
34	69	M	Normal PR, QRS, and axis	705	910	242	150	460	310	320	320
35	69	F	Supraventricular tachycardia	715	1010	135	200	215*	230	140	240
			Mean ± SD	766 ± 102	860 ± 107	164 ± 49	182 ± 49	247 ± 113	284 ± 115	235 ± 137	262 ± 10

*Longest escape sinus cycle was 2nd or 3rd cycle.
AP, atrial pacing; CL, cycle length; ND, not definable.

With propranolol, the increase (15%) in mean corrected sinus node recovery time (from 247 to 284) after atrial pacing at a cycle length of 500 ms was statistically significant ($P < 0{\cdot}025$). However, the increase in corrected sinus node recovery time (from 235 to 272 ms) after atrial pacing at a cycle length of 430 ms was not statistically significant. In addition, when the data of maximum or the longest corrected sinus node recovery time at either of the atrial pacing cycle lengths are reviewed, the maximum time: (a) increased from a mean of 284 ± 130 to 317 ± 112 ms and (b) lengthened in 25 and shortened in 10 patients after propranolol. In this study of patients with normal sinus node function, there was no difference in response to propranolol related to the presence or absence of associated arrhythmias.

Discussion

In the past 6 years, atrial pacing studies have been extensively used for electrophysiological evaluation of sinus node function in man, both for investigative and clinical purposes. With the increasing use of such techniques, it has become apparent that at times in patients with previously documented sinus node dysfunction, the evaluation of sinus node function by electrophysiological means is within normal limits at the time of the study. These observations raise questions as to whether the electrophysiological testing procedures are inadequate and unreliable or whether the laboratory results return to normal because of an increase in release of stored catecholamines resulting from the stress of cardiac catheterisation. If the latter possibility is true, then it may be argued that patients requiring evaluation of sinus node function for clinical purposes may be analysed with greater accuracy by blocking the effect of increased catecholamines with propranolol administration.

Recently Strauss *et al.* (1976b) attempted to evaluate this consideration in 10 patients who were thought to have symptomatic sinus node dysfunction. However, only 2 of the 10 patients had abnormal corrected sinus node recovery time during control and both showed a severe prolongation of corrected sinus node recovery time after propranolol. In 5 other patients, the corrected sinus node recovery time changed by ≤ 58 ms with propranolol. Since the effect of propranolol on normal sinus node function was not known, their observations cannot be reviewed from a proper perspective and have failed to satisfy the questions raised above. Their study left several questions unanswered. Does propranolol have a significant effect on sinus node recovery time in both patients with normal and abnormal sinus nodes? Is the severe prolongation of sinus node recovery time noted in 2 of the 10 cases an unusual response, or is it indicative of severe sinus node dysfunction?

Our data in patients with normal sinus node function show that with propranolol sinus cycles lengthened significantly ($P < 0{\cdot}005$) with an average increase of 12 per cent. This prolongation in sinus cycle length is slightly less as compared with 16 per cent (Seides *et al.*, 1974) and 22 per cent (Stern and Eisenberg, 1969) reported by others. The difference between our results and those of others may be explained by the fact that our patients were premedicated with pentobarbitone sodium whereas others obtained their data in non-sedated patients, possibly with higher levels of released catecholamines. The greater the beta-adrenergic stimulus, the greater the response to beta-adrenergic blockade. In our patients, the control sinus cycle lengths noted at the time of the study were usually similar to those noted on routine electrocardiograms. This suggests that possibly there was no obvious increase in catecholamine release during the electrophysiological study.

After propranolol, though the mean corrected sinus node recovery time lengthened after each of the atrial pacing levels (120/min and 140/min), it was statistically significant only after atrial pacing at 120/min. In addition, in 49 per cent of the patients the corrected sinus node recovery time, at either of the pacing cycle lengths, decreased after propranolol. Previous studies (Breithardt and Seipel, 1976) have indicated a faster conduction into the sinus node with sympathetic stimulation or with parasympathetic blockade after atropine. Therefore, the converse is also possible, that is an increased conduction delay or entrance block into the sinus node with sympathetic blockade. A decrease in corrected sinus node recovery time with propranolol may be explained on the basis of an enhanced entrance block into the sinus node and which, compared with the control levels, was manifested in some at lower atrial pacing rates. However, a lack of significant increase in sinuatrial conduction time with propranolol fails to support such a possibility.

If, in fact, propranolol enhances entrance block into the sinus node, it may possibly obscure the demonstration of sinus node dysfunction and may mask prolongation of the sinuatrial conduction time. Recently reported observations (Strauss *et al.*, 1976b) of a distinct prolongation of corrected sinus node recovery time with propranolol in some and not all of the cases with clinically diagnosed sinus node dysfunction may suggest that: (a) if in patients with sinus node dysfunction, as discussed above, a protection from overdrive suppression does exist, it does not apply to all of the cases with sick sinus node; and (b) depending upon the response to propranolol, it may be possible to differentiate the various underlying mechanisms responsible for sick sinus syndrome, that is abnormalities of sinuatrial conduction and of the generator function of the sinus node.

During experiments in isolated tissues, it has been previously noted (Rosenbleuth, 1950) that in order to produce slower sinus rates or asystole it is necessary to affect all sinus node pacemaker fibres by acetylcholine, whereas only a few sinus node pacemaker fibres need be accelerated by norepinephrine to produce an increment in the heart rate. Therefore, it may be reasoned that in patients with sick sinus node, only a few sinus node pacemaker fibres may be functioning under the influence of available catecholamines which are sufficient to sustain sinus rhythm. In such patients, a withdrawal of catecholamine influences and beta-adrenergic blockade with propranolol may not only result in slower sinus node rates but also show a pronounced suppression to overdrive pacing or a distinct prolongation of the sinus node recovery time.

In our series, the maximum corrected sinus node recovery time at either of the atrial pacing rates showed a mean prolongation of 33 ms (11%) with propranolol. None of the patients showed a severe prolongation in corrected sinus node recovery time similar to that observed by Strauss *et al.* (1976b) in 2 of their 10 cases with sinus node dysfunction. On the basis of present data, it may be suggested that in the dosage used in this study and in therapeutic doses, propranolol may be safely administered when required to patients with electrophysiologically normal sinus node function without affecting it adversely. Accordingly, the evaluation of sinus node recovery time with and without propranolol may be clinically useful, before the institution of propranolol therapy, for detecting patients in whom a distinct adverse effect on sinus node function may occur, though extrapolation to patients on long-term oral treatment with propranolol may not be valid.

In all but 4 of the cases in our series, the first escape sinus node cycle after cessation of atrial pacing was the longest, both during control and after propranolol. This suggests that the secondary pauses are not common in cases with normal sinus node function and, when noted, may be suspicious of an overt or latent sinus node dysfunction. It may also be indirectly concluded that after propranolol administration a conversion of supraventricular tachycardia when associated with a long period of asystole probably indicates a sick sinus node. The asystole should not be interpreted merely as an expected side effect of propranolol. Such patients should be further investigated, in the absence of propranolol to confirm the diagnosis of sick sinus syndrome.

Previous workers (Breithardt and Seipel, 1976) have shown that sinuatrial conduction time is affected by autonomic influences, that is shortened by parasympathetic blockade or sympathetic stimulation. Our data show that though after propranolol there was a slight increase in the mean sinuatrial conduction time for the entire group, it was not statistically significant. It is difficult to evaluate properly the effect of propranolol on sinuatrial conduction time because of the limitations inherent in the present technique for its estimation (Strauss and Wallace, 1976).

The dosage of propranolol used in this study is similar to that used by others during electrophysiological studies in man (Seides *et al.*, 1974; Strauss *et al.*, 1976b). Propranolol in these doses produces 20 to 30 per cent blockade of exercise-induced sinus tachycardia and requires a tenfold increase in the dose of isoprenaline to produce a given level of sinus tachycardia (Coltart and Shand, 1970). The plasma level resulting from this dosage regimen has been shown to have a significant beta-adrenergic blocking effect. Mean serum levels of 13·6 ng/ml have been reported 45 to 60 minutes after propranolol administration with this dosage regimen (Seides *et al.*, 1974). Our studies were generally completed within 30 min of the last dose of propranolol. In addition, this dosage regimen was selected to avoid unnecessary side effects or complications, that is hypotension which in turn may artificially alter the sympathetic and parasympathetic influences and thereby confuse the interpretation of the results. The results of the present study of an increase in sinus node cycle length, lengthening of corrected sinus node recovery time, and a possible prolongation of sinuatrial conduction time may all be explained on the basis of the beta-adrenergic blocking effect of propranolol on the sinus node and the atrial myocardium.

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Comparability and reproducibility of apex cardiogram recorded with six different transducer systems[1]

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SUMMARY A comparison was made in 7 dogs of the results obtained by 6 different apex cardiographic transducers applied before, during, and after controlled infusion of angiotensin and isoprenaline.

The electrocardiogram, internal phonocardiogram, aortic and left ventricular pressure using a Telco micromanometer, and apex cardiogram were recorded simultaneously on magnetic tape and paper. Digital computer techniques were used to derive various measurements. The comparison of the 6 transducer systems was made especially with respect to measurements derived from the normalised derivative, calculated using total as well as developed pressure or displacement.

Measurements derived from left ventricular pressure were very reproducible. Differences in results of 'contractility' indices varied between 0·5 and 1·9 per cent. Indices from the apex cardiogram using 6 different transducer systems showed variations up to 20 per cent, with mean values varying between 3·2 and 8·1 per cent. There was a systematic deviation for one transducer system, which was responsible for a significant part of the observed variability.

It may be concluded that in order to assure maximal reproducibility, technical characteristics of the apex cardiograph transducer should be taken into account and an optimal recording technique should be used.

Reproducibility of results is a prerequisite for any method to have scientific value. Many authors have noted that certain morphological features of the apex cardiogram are consistent, when recordings are made at different intervals in time (Hartman and Snellen, 1960; Benchimol and Dimond, 1963; Tavel, 1967; Wayne, 1970; Craige, 1973). However, few systematic studies have been performed on the reproducibility of the apex cardiogram. In none has the apex cardiogram been recorded with different transducer systems (Ginn *et al.*, 1967; Gleichmann, 1968; Motomura *et al.*, 1973; Willems, 1973; Denef *et al.*, 1975; Dübel *et al.*, 1975).

In the present study reproducibility of the apex cardiogram has been tested under well-controlled laboratory conditions. Our objective was to examine the variability resulting from differences in physical characteristics of various transducer systems. A comparison was made of results obtained by 6 different apex cardiographic transducers, applied consecutively, before, during, and after controlled infusion of angiotensin and isoprenaline in 7 dogs. Studies were made particularly of measurements derived from the normalised apex cardiogram derivative, since in recent years increased attention has been given to these measurements in the non-invasive assessment of left ventricular function (Reale, 1967; Gleichmann, 1968; Fincker *et al.*, 1971; Mirsky *et al.*, 1972; Vetter *et al.*, 1972; Denef *et al.*, 1973; Willems, 1973; Denef *et al.*, 1975; Willems *et al.*, 1975).

Methods

MATERIAL AND RECORDING TECHNIQUE

The experiments were performed in 7 dogs weighing 27 to 32 kg and anaesthetised by subcutaneous adminstration of a combination of fluanisone (4 mg/kg) and fentanyl base (0·1 mg/kg) (Hypnorm, Philips-Duphar) followed 30 minutes later by the intravenous injection of sodium pentobarbitone (13 mg/kg), with repeat injections when needed. Artificial positive pressure respiration was instituted through a tracheal cannula by means of a

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Bird respirator and ventilated with a mixture of room-air (60%) and oxygen (40%).

The apex cardiogram was recorded in the left recumbent position and in expiratory apnoea. Three of the apex cardiograph pick-ups were pressure- and 3 were displacement-measuring devices. Application pressure could be assessed with the fluid pressure—but not with the displacement-transducer systems. All pulse transducers were held by hand at the point of maximal impulse and the recordings were made under oscilloscopic control by the same observer.

MEASUREMENT SYSTEMS

Essentially two different methods exist to record the apex cardiogram. In displacement apex cardiography free movement of the apical impulse is recorded in relation to the rim of the recording device or to a fixed point in space. In pressure apex cardiography a counter pressure is applied on the thoracic wall and transducer systems are used with a rigid sensing apparatus, so that displacement is as small as possible.

The transducer systems used in this study were the following:

(1) A fluid-filled, calibrated pressure measuring system, with a membrane diameter of 8 mm (Wesseling and Van Vollenhoven, 1969; Willems *et al.*, 1971a, 1972; Denef *et al.*, 1973; Willems, 1973; van de Werf *et al.*, 1976).

(2) A Marey capsule, connected by plastic tubing (25 cm long and 4 mm internal diameter) and air transmission to a sensitive Elema EMT 42 pressure transducer (Elema-Schönander, Stockholm) (Kesteloot *et al.*, 1969; Willems, 1973).

(3) The 'conventional' Marey system consisting of a Marey capsule coupled to a piezoelectric microphone (Kesteloot *et al.*, 1969).

(4) A new quantitative displacement measuring system, built in an open ended pick-up capsule (Elema-Schönander, Stockholm) (Nillsson and Thulesius, 1973; Denef *et al.*, 1975).

(5) Same transducer system as no. 1, with a membrane of 6 mm (Willems, 1973; Denef *et al.*, 1973).

(6) A variable inductance pick-up (Telco, Paris) described by Tricot *et al.* (1966). This contacting transducer is in fact a modified micromanometer with a rigid sensing head.

Transducer systems 1, 2, and 5 are experimental systems developed and tested in our institution. Systems 3, 4, and 6 are commercially available and used in continental Europe and to some extent also in the USA.

The air-coupled crystal microphone systems (systems 3 and 4) had a time-constant, respectively, of 2·5 and 4 seconds. The time constant of the others was infinite. Response characteristics for high frequencies were variable and have been published previously for all but one system (Tricot *et al.*, 1966; Kesteloot *et al.*, 1969; Wesseling and Van Vollenhoven, 1969; Willems *et al.*, 1971a, b, 1972; Denef *et al.*, 1973; Nillsson and Thulesius, 1973; Willems, 1973; Denef *et al.*, 1975; Willems *et al.*, 1975; van de Werf *et al.*, 1976).

Pick-up number 1 has been tested by Wesseling and Van Vollenhoven (1969) using a vibrator and the step technique. The response was found to be linear between 0 and 15 Hz. At 20 Hz, a 15 per cent increase in response was noted and the resonance frequency was at 60 Hz. The damping coefficient was 0·075, which points to an underdamped system, as is often the case with fluid-filled catheter-manometer systems (Wesseling and Van Vollenhoven, 1969; Willems, 1973). The DC Marey system has a flat response from 0 to over 100 Hz (Kesteloot *et al.*, 1969). The output of pick-up number 3 was linear between 0·05 Hz (−3db point) and 50 Hz (10% overshoot) (Kesteloot *et al.*, 1969). The upper and lower −3db point attenuation limits of the unfiltered output of transducer number 4, used in the present study, are at, respectively, 1000 Hz and 0·04 Hz (Nillsson and Thulesius, 1973; Denef *et al.*, 1975). The resonance frequency of the water-filled pulse transducer with a membrane of 6 mm lies at 40 Hz (A. Aubert and J. Joossens, unpublished findings), whereas the inductance pick-up has a flat response between 0 and 1000 Hz (Tricot *et al.*, 1966).

RECORDING PROCEDURES

The 6 transducers were applied in a semirandom order, first during basal conditions, next 15 minutes after a constant infusion by means of a Harvard pump of a low dosage of isoprenaline (0·022 ± 0·011 gamma/kg per min). Thereafter a return to the basal state was allowed during ± 15 minutes, after which 6 more control recordings were made. Finally angiotensin was given at a rate of 0·019 ± 0·013 gamma/kg per min and the measurements were repeated.

Since application of each of the different apex cardiographic systems took on the average 4 to 5 minutes, one observation period for all 6 transducers lasted 20 to 30 minutes. Because of technical problems with the tape-recording, 2 of the 168 registrations could not be analysed, so that paired comparison between each of the 6 transducers could be made in 26 of the 28 observation periods.

MEASUREMENTS

The electrocardiogram (lead II), internal phonocardiogram, aortic and left ventricular pressure, using Telco micromanometers, and the apex cardiogram were recorded simultaneously on frequency modulated magnetic tape and paper. Digital computer techniques were used to derive various measurements and to calculate median values on the beats present in 15 seconds of recording, as described previously (Willems, 1973, 1974). Conversion of the analogue data to digital form was carried out at a sampling rate of 250 samples/s. All analyses were done on an HP 2100 computer system.

The comparison of the 6 apex cardiographic transducer systems was made especially with respect to different measures of the rate of rise of the apex cardiogram and left ventricular pressure. The normalised derivative, that is the velocity of rise of the curve divided by its amplitude, was calculated using total as well as developed pressure (dP/dt/P) or displacement (dD/dt/D).

The first derivative was digitally derived from the apex cardiogram and pressure curves using a first difference method:

$$(dP/dt)_n = (P_{n+1} - P_{n-1})/(t_{n+1} - t_{n-1}),$$

whereby P_{n-1}, P_n, and P_{n+1} are any 3 consecutive pressures, or displacement measurements in case of displacement apex cardiograms measured 4 ms apart at times t_{n-1}, t, and t_{n+1}.

The derivation of $(dP/dt)/(kP + c)$, $(dP/dt)/kP$ and $(dP/dt/P)$, with $k = 32$, as approximations of contractile element shortening velocity during isovolumic systole has been discussed by several authors (Mason *et al.*, 1970; Falsetti *et al.*, 1971). In analogue to the derivation from left ventricular pressure data we have calculated similar indices from the apex cardiogram.

Since no real zero reference level exists in apex cardiography, the level of the 0 point was used as a substitute for the determination of total pressure or displacement, whereas the C point was used as reference for developed apical displacement or pressure.

Force velocity curves were obtained by plotting $(dP/dt)/P_{dev}$ and $(dP/dt)/P_{total}$ data on the ordinate versus, respectively, developed and total pressure or displacement, on the abscissa, for every separate beat and for a composite of all beats present in the recording. Straight line fitting was done through the points of the descending portion of the force velocity curve in case of total pressure or displacement. V_{max} was obtained by extrapolation to zero in case of developed pressure or displacement by means of a polynomial curve fitting routine of degree one and degree two. V_{max} and V_{CE} data are expressed in units per second denoted as s^{-1}.

When normalised derivatives are digitally computed the sensitivity at which apex cardiograph curves are recorded does not influence the result, thereby allowing calculation of these indices from calibrated as well as from non-calibrated recordings.

Total diastolic deflection of the apex cardiogram was determined in the conventional manner (Benchimol and Dimond, 1963; Tavel, 1967) by measuring the vertical distance between the beginning of the upstroke (C point) and nadir of the curve (0 point) as a percentage of the total height of the curve. The time intervals from the C to 0 point and from C to the peak of derivative of the apex cardiogram and left ventricular pressure curve have also been calculated.

Whenever indices were computed from single beats a representative value for the recording period was computed by deleting the two values most extremely located from the median and averaging the results of the remaining beats. Since differences between V_{max} values obtained in this manner from individual beats and from a composite of beats were insignificant, only V_{max} values obtained with the latter method are reported in this study.

STATISTICAL ANALYSES

For each haemodynamic intervention, averages and standard deviations were calculated for each of the various measurements on corresponding apex cardiographic and left ventricular pressure data.

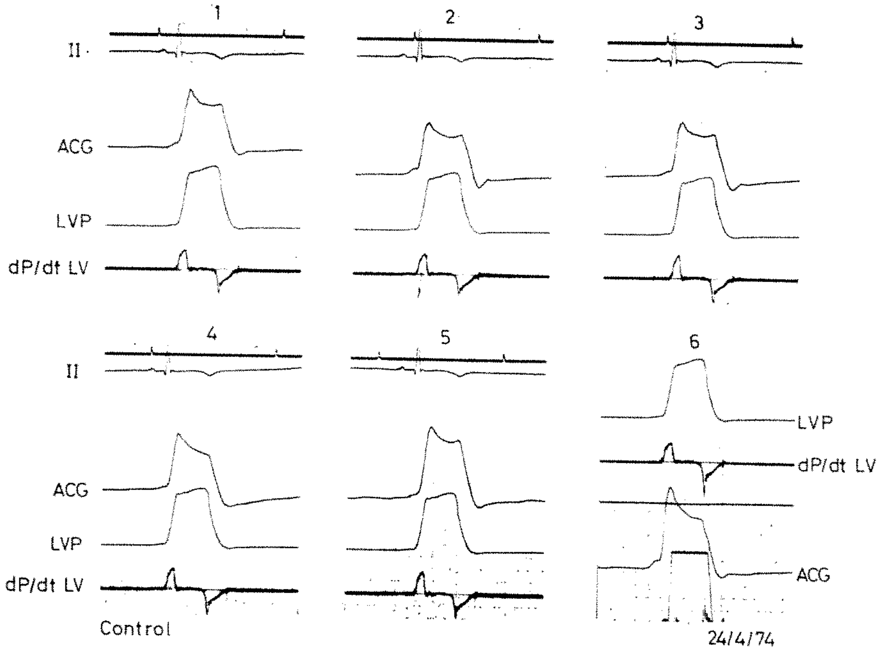
Pooled data from all recording sessions were used to compute mean differences and paired t tests in the comparison of the 6 different apex cardiograph transducer systems.

Variability of the results was tested by calculating the deviations from the average in each observation period and expressing the results as percentages. The average of the 6 results obtained in each observation period for each measurement from the apex cardiogram and corresponding left ventricular pressure was taken as 100 per cent. In this way variability of measurements of different nature, for example left ventricular systolic pressure and peak (dP/dt/P), or magnitude could be compared.

Results

AMPLITUDE MEASUREMENTS AND TIME INTERVALS

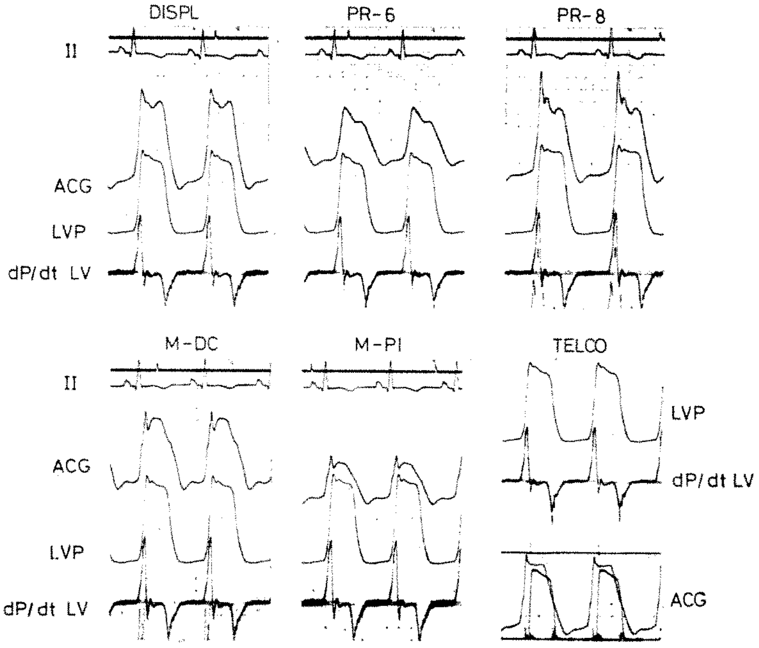
Apex cardiograms taken with the 6 transducer systems during control conditions and during isoprenaline and angiotensin administration are illustrated in Fig. 1-3. The tracings were comparable with respect to their morphological appearances. Variable recordings, however, could be obtained with only minimal changes in location of the pick-up, as shown in Fig. 4.



Control

24/4/74

Fig. 1 *Representative tracings obtained with the 6 different transducer systems during control conditions. For pick-up identification see Methods. Abbreviations: ACG, apex cardiogram; LVP, left ventricular pressure; dp/dt LV, first derivative of left ventricular pressure.*



Isoprenaline

12/4/74

Fig. 2 *Representative tracings obtained with the 6 different transducer systems during isoprenaline infusion. Abbreviations: see legend Fig. 1; DISPL, displacement transducer no. 4; M-DC, Marey DC, M-PI, Marey piezoelectric; PR-6 and PR-8, fluid-filled pressure transducer with membrane of, respectively, 6 and 8 mm.*

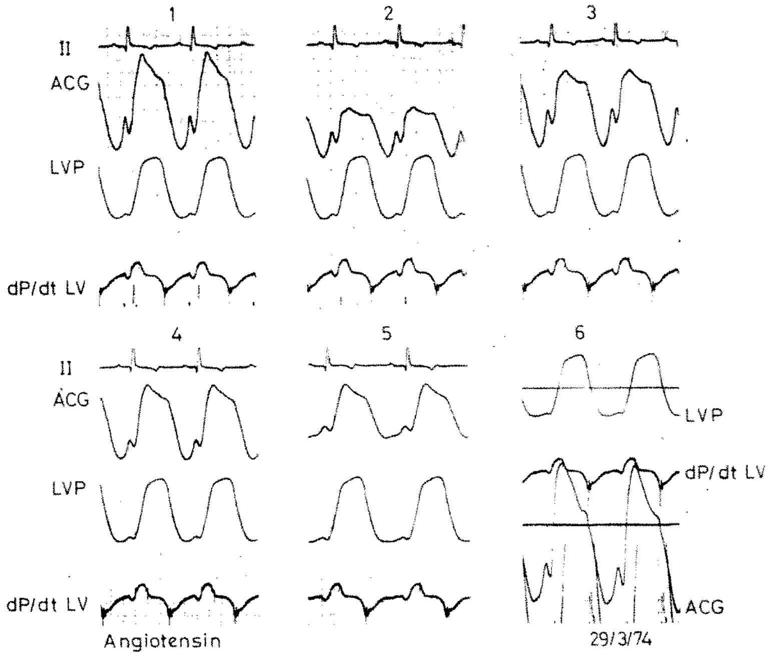


Fig. 3 *Representative tracings obtained with the 6 different transducer systems during angiotensin administration. Abbreviations: see Fig. 1.*

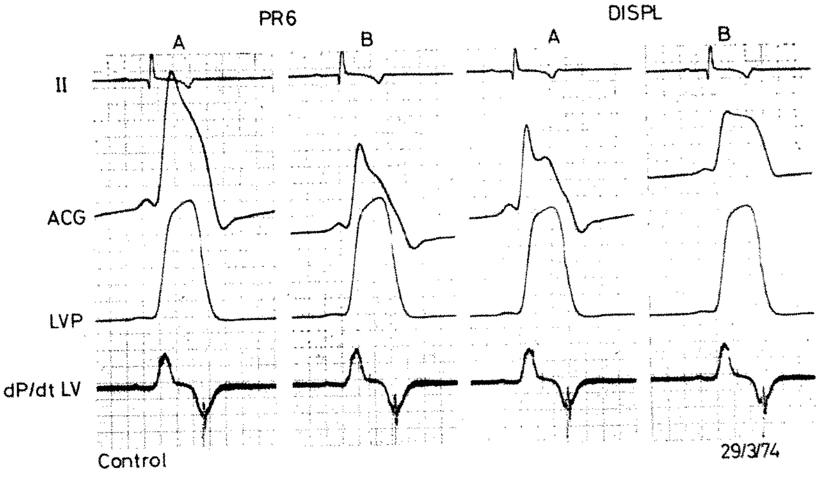


Fig. 4 *Illustration of variability in apex cardiograph morphology, especially of the systolic plateau, as a result of only minor displacement of the pick-up location. Abbreviations: see Fig. 2.*

Mean values of total diastolic deflection, expressed as a percentage of the total apex cardiograph height, are given in Table 1, for each of the pick-up systems. The values obtained with the displacement measuring systems (transducers 2, 3, and 4) were significantly higher ($P < 0.01$) than those obtained with the pressure measuring devices (transducers 1, 5, and 6).

Small insignificant differences could be demonstrated in the C to 0 time intervals. The apex cardiograms recorded with the pressure measuring transducer, equipped with a sensing diameter of

Table 1 *Comparison between total diastolic deflections and time intervals derived from 6 apex cardiographic transducer systems and corresponding left ventricular systolic and end-diastolic pressure and peak time*

	Apex cardiographic transducer system						*Statistically significant differences between results*		
	1	*2*	*3*	*4*	*5*	*6*	$P < 0{\cdot}001$	$P < 0{\cdot}01$	$P < 0{\cdot}05$
Apex cardiogram									
Total diastolic deflection %	19·8 (1·4)	26·4 (1·8)	26·2 (1·8)	23·2 (1·8)	19·2 (1·1)	21·4 (1·4)	1-3; 2-5 3-5; 3-6	2-6	1-4; 4-5
C—to peak derivative (ms)	29·7 (1·8)	30·7 (2·0)	31·1 (1·6)	31·3 (1·7)	36·6 (1·5)	31·8 (1·9)	1-5	3-5	2-5; 4-5 5-6
C-0 interval (ms)	399 (15)	391 (14)	396 (17)	394 (12)	395 (11)	401 (15)			1-2
Heart rate (beats/min)	76·2 (4·1)	77·0 (4·6)	77·1 (4·7)	76·8 (4·5)	76·7 (4·1)	78·4 (4·5)			
LV pressure									
Syst. press. (mmHg)	135·9 (6·9)	135·3 (6·9)	135·5 (7·1)	135·2 (7·1)	133·5 (6·8)	137·0 (7·1)			
LVEDP (mmHg)	11·8 (1·2)	12·0 (1·4)	11·0 (1·3)	11·4 (1·5)	11·0 (1·3)	11·1 (1·4)			
C—to peak derivative (ms)	53·4 (1·6)	52·1 (1·5)	53·6 (1·7)	53·5 (1·6)	54·6 (1·8)	54·4 (2·0)			

Methods: (1) pressure (8 mm); (2) Marey DC; (3) Marey piezo; (4) displacement; (5) pressure (6 mm); (6) Telco pick-up.
Total number of paired observations, 26; LVDEP, left ventricular end-diastolic pressure.
Mean and standard errors of the mean (between parentheses) are given.

Table 2 *'Contractility' indices derived from left pressure data and the apex cardiogram, recorded by 6 different transducers: means and standard errors are given ($N = 26$ paired observations)*

	Transducer					
	1	*2*	*3*	*4*	*5*	*6*
LV pressure						
dP/dt max	2257 (151)	2296 (160)	2347 (171)	2281 (160)	2273 (157)	2310 (174)
peak ($dP/dt/P_T$)	60·5 (1·5)	59·7 (1·5)	61·8 (2·0)	59·8 (1·8)	61·3 (1·6)	60·3 (1·4)
V_{max} tot P	1·97 (0·05)	1·97 (0·05)	2·00 (0·05)	1·98 (0·05)	1·96 (0·05)	1·98 (0·06)
V_{max} dev P						
– lin	3·50 (0·08)	3·51 (0·07)	3·51 (0·10)	3·46 (0·08)	3·48 (0·08)	3·40 (0·08)
– poly	4·54 (0·11)	4·53 (0·10)	4·50 (0·14)	4·42 (0·11)	4·44 (0·09)	4·31 (0·10)
Apex cardiogram						
peak ($dP/dt/P_T$)	43·1 (2·2)	38·9 (2·2)	39·0 (2·2)	39·9 (2·1)	37·8 (1·6)	40·4 (2·0)
V_{max} tot P	2·50 (0·14)	2·37 (0·10)	2·27 (0·10)	2·16 (0·10)	1·81 (0·09)	2·16 (0·10)
V_{max} dev lin	4·65 (0·16)	4·85 (0·14)	4·67 (0·17)	4·35 (0·14)	3·58 (0·14)	4·22 (0·15)
V_{max} dev poly	5·94 (0·19)	6·34 (0·25)	6·00 (0·25)	5·59 (0·19)	4·50 (0·20)	5·45 (0·23)

Transducer systems: (1) pressure (8 mm); (2) Marey DC; (3) Marey piezo; (4) displacement; (5) pressure (6 mm); (6) Telco pick-up.
P, pressure; tot, total; dev, developed; lin and poly, respectively linear and polynomial fitting (see Methods); P_T, total pressure.

6 mm, had a significantly longer C to peak time, as shown in Table 1.

INDICES DERIVED FROM NORMALISED DERIVATIVE

Measures derived from left ventricular pressure data were very reproducible (Table 2). The maximal difference in any of the 6 recordings obtained during application of the 6 different apex cardiographic transducer systems was 3·4 per cent, namely for left ventricular end-diastolic pressure. Variability in 'contractility' measurements derived from left ventricular pressure averaged between 0·5 and 1·9 per cent (Table 3).

Indices derived from the apex cardiogram using 6 different transducer systems showed a significantly greater variability (Table 2). The average variation from the mean for different measurements varied between 3·2 and 8·1 per cent (Table 3). One system showed average deviations from the mean up to 20 per cent. The results obtained with this pick-up (no. 5) were significantly different from the others.

Table 3 *Average results and deviations from mean, in absolute values (△) and as relative differences (%) for each of 6 different apex cardiographic transducer systems, using pooled data ($N = 26$ observation periods)*

Measurement	*Left ventricular pressure*		*Apex cardiogram*		*Mean deviations for each apex cardiographic transducer system*						
	Global mean	*Variability %*	*Global mean*	*Variability %*	*1*	*2*	*3*	*4*	*5*	*6*	
V_{max} (total P)	1·98		2·21		0·29	0·16	0·06	−0·05	−0·40	−0·05	Δ
		0·5		7·6 (5·0)*	(13·1)	(7·2)	(2·7)	(2·3)	(18·1)	(2·3)	%
V_{max} (dev P) – lin	3·48		4·39		0·26	0·46	0·28	−0·04	−0·81	−0·17	Δ
		0·9		7·7 (4·6)	(5·9)	(10·5)	(6·4)	(0·9)	(18·5)	(3·9)	%
– poly	4·46		5·64		0·30	0·70	0·36	−0·05	−1·14	−0·19	Δ
		1·5		8·1 (4·7)	(5·3)	(12·4)	(6·4)	(0·9)	(20·2)	(3·4)	%
Peak dP/dt/P	60·6		39·9		3·25	−0·95	−0·85	0·05	−2·05	0·55	Δ
		1·2		3·2 (3·0)	(8·2)	(2·4)	(2·1)	(0·1)	(5·1)	(3·2)	%
Peak time (ms)	53·6		31·9		−2·2	−1·2	−0·8	−0·6	4·7	−0·1	Δ
		1·1		5·0 (2·9)	(6·9)	(3·8)	(2·5)	(1·9)	(14·7)	(0·3)	%
Total diastolic deflection (%)	6·1		22·7		−2·9	3·7	3·5	0·5	−3·5	−1·3	Δ
		1·9		11·3 (9·9)	(12·8)	(16·3)	(15·4)	(2·2)	(15·4)	(5·7)	%

Methods: (1) pressure (8 mm); (2) Marey DC; (3) Marey piezo; (4) displacement; (5) pressure (6 mm); (6) Telco.
*Average variability data, expressed as per cent, after deleting results of pick-up 5.

Table 4 *Mean absolute differences ($\bar{D}$) in peak dP/dt/P values obtained by 6 different apex cardiograph transducer systems and corresponding paired t tests*

Method	*2*	*3*	*4*	*5*	*6*
1	4·21 (1)	4·06	3·25	5·33	2·69
	1·68 (2)	1·49	1·69	2·64*	1·58
2		−0·15	−0·96	1·12	−1·52
		−0·09	−0·39	0·46	−0·79
3			−0·81	1·27	−1·37
			−0·35	0·44	−0·64
4				2·08	−0·56
				1·15	−0·30
5	(1) mean differences ($\bar{D}$)				−2·63
	(2) paired t tests				−1·22

Methods: (1) pressure (8 mm); (2) Marey DC; (3) Marey piezo; (4) displacement; (5) pressure (6 mm); (6)Telco.
*Significance level : $P < 0·05$.
Standard deviations ($S_{\bar{D}}$), not presented in this and following table, can be derived using the formula

$$S_{\bar{D}} = \frac{\bar{D}}{t}$$

Total number of paired observations.

Table 5 *Mean absolute differences between so-called V_{max} indices† using total pressure or displacement obtained by 6 different apex cardiograph pick-up systems*

Method	*2*	*3*	*4*	*5*	*6*
1	0·13 (1)	0·23	0·34	0·69	0·34
	1·14 (2)	1·55	2·77*	5·12***	2·63
2		0·11	0·21	0·57	0·21
		1·37	2·64*	5·53***	2·05
3			0·10	0·46	0·10
			1·13	3·99***	1·28
4				0·36	0·003
				3·42**	0·03
5	(1) mean differences ($\bar{D}$)				−0·35
	(2) paired t tests				−3·33**

Methods: (1) pressure (8 mm); (2) Marey DC; (3) Marey piezo; (4) displacement; (5) pressure (6 mm); (6) Telco.
* $P < 0·05$; ** $P < 0·01$; *** $P < 0·001$.
†Using (dP/dt)/kP_{tot} with $K = 32$.
Total number of paired observations: 26.

A significant part of the observed variability was due to this pick-up (Table 2). By deleting transducer no. 5, variability for different measurements decreased significantly to an average of 2·9 to 5·6 per cent (Table 3).

The most consistent results were obtained for peak (dP/dt/P). Two matrices with mean differences and corresponding paired t tests of measurements derived from the apex cardiogram, recorded with the 6 different recording systems, are given in Tables 4 and 5. Most differences in these and other comparisons were not significant except for pick-up 5.

CORRELATION BETWEEN LEFT VENTRICULAR PRESSURE AND APEX CARDIOGRAPHIC INDICES

Correlations were calculated between various indices derived from the normalised apex cardiographic derivative and corresponding left ventricular pressure measures for each of the 6 different apex cardiographic transducer systems. Correlation coefficients varied between 0·35 and 0·72. None of the 6 transducer systems showed a superiority in this respect. The highest correlations in the present investigation were found between left ventricular pressure and apex cardiographic 'contractility' indices, using developed pressure or displacement.

Discussion

Whereas previous authors (Ginn *et al.*, 1967; Gleichmann, 1968; Motomura *et al.*, 1973; Willems, 1973; Denef *et al.*, 1975; Dübel *et al.*, 1975) have tested the reproducibility of the apex cardiogram using the same transducer applied on the same subjects at different time intervals, in the present study we analysed the comparability and reproducibility of the apex cardiogram recorded with 6 different transducer systems.

REPRODUCIBILITY USING SAME TRANSDUCER

Ginn *et al.* (1967) have studied day-to-day reproducibility of the A wave in the resting and post-exercise apex cardiogram. Apex cardiograms were recorded on 3 different days in 24 normal subjects and in 22 patients with ischaemic heart disease. Though the coefficient of variation, defined as the standard error deviation within subjects divided by the mean of the group, was relatively high (between 28 and 33%), the authors concluded that reproducibility was not an important limiting factor to the discriminatory ability of the method.

A systematic study on reproducibility of 21 different measurements, including some indices derived from the first derivative of the apex cardiogram, has been published by Dübel *et al.* (1975). Recordings were made in 15 subjects at 4 different time intervals, two the first day, 10 minutes apart, the third and fourth, respectively, 2 and 10 days later. Analysis of variance was done and all F-tests were below 2·7, which was the 5 per cent significance level.

Inter- and intraobserver variation on the calibrated derivative from the apex cardiogram has been studied by Denef *et al.* (1975). The intraobserver variation was determined in 23 subjects by recording the apex cardiogram twice with the same transducer, within an interval of at least one week. The variation was 11 to 25 per cent for data derived from the normalised apex cardiogram derivative. Variability results between 28 and 44 per cent were obtained for non-normalised amplitudes.

An average relative difference of 8 per cent in peak normalised derivative values was found by Motomura *et al.* (1973) in 16 patients, with apex cardiograms recorded at one- or two-week intervals, using the same equipment.

COMPARABILITY OF APEX CARDIOGRAM RECORDED WITH DIFFERENT TRANSDUCERS

Within the same laboratory results may be reproducible, but this may not be so between different laboratories. Indeed, comparison of morphological features of apex cardiograms, recorded in different laboratories, has been difficult in the past (Craige, 1973). This resulted mainly from the use of varying techniques and of transducer systems unsuitable for recording low frequency vibrations (Reale, 1967; Johnson *et al.*, 1971; Willems, 1973). It is now widely accepted that transducers should be used with an adequately long time constant, of at least 2·5 s, the ideal being an infinite time constant (Wesseling and Van Vollenhoven, 1969; Johnson *et al.*, 1971; Willems, 1973; Reddy *et al.*, 1976).

In the present study a comparison was made of results obtained with 6 different apex cardiographic transducer systems, obeying this requirement. Reproducibility was tested under well-controlled laboratory conditions. Recordings were made before, during, and after controlled infusion of angiotensin and isoprenaline in 7 dogs. Our objective was to examine variability, as a result solely of differences in apex cardiograph transducer systems. In particular, indices derived from the normalised derivative have been analysed. Analysis of the recordings was done entirely by computer techniques, thereby eliminating observer measurement variability.

Measures derived from left ventricular pressure were very reproducible. Variability in results of 'left ventricular pressure contractility' measures averaged 0·5 and 1·9 per cent. This proves that during the recording sessions the haemodynamic status of the animals was stable and that the computer techniques used for calculating did not introduce any appreciable degree of variation.

Indices derived from the apex cardiogram, using 6 different transducer systems, showed significantly greater variations, with mean results varying between 3·2 and 8·1 per cent. One pick-up showed deviations up to 20 per cent from the pooled mean data. Deleting results of this device decreased significantly the variability, to an average of 2·9 to 5·0 per cent for indices derived from the normalised derivative.

Results on peak (dP/dt/P), respectively peak (dA/dt/A), were most consistent. If we take the mean obtained with all 6 transducers as the 'real' peak (dP/dt/P) value, then deviations from this average varied between 0·1 and 8·2 per cent (mean 3·2). Most of the differences between results obtained with the different transducers were not significant, except for one transducer system.

DETERMINING FACTORS OF VARIABILITY

Derivation of measurements from the normalised derivative with regard to total pressure is dependent on the total height of the diastolic deflection.

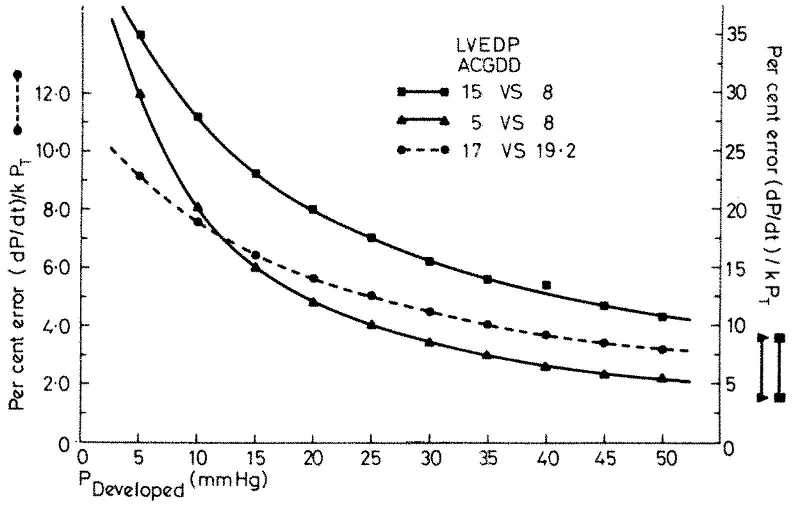


Fig. 5 *Graphic representation of the error, in per cent, of (dP/dt)/P ratios introduced by using incorrect left ventricular end-diastolic pressures (LVEDP) or wrong apex cardiographic diastolic deflections (ACGDD) of the apex cardiogram. The full line denoted by squares indicates the underestimation introduced when 15 mmHg is used instead of 8 mm as LVEDP. The two other lines illustrate the overestimation when values of 5 and 17 are used instead of, respectively, 8 and 19·2. The highest errors in (dP/dt)/P ratios are found at low developed pressures.*

Errors in the determination of this measurement largely influence peak (dP/dt/P) and so-called V_{max} indices derived from total pressure, especially when end-diastolic deflections are low, as shown in Fig. 5. The derivation of measurements from the normalised apex cardiogram derivative, therefore, requires that the time-constant of the apparatus should be long, that is at least 2·5 to 5 seconds, otherwise variable differentiation will take place with changes in the RR interval. With varying diastolic periods the total diastolic deflection might be artificially different, thereby influencing (dP/dt/P) or (dA/dt/A) ratios.

Total diastolic deflections of the apex cardiograms recorded in the present study with displacement measuring systems were significantly higher than in apex cardiograms recorded with pressure measuring systems, though the time constant of all systems exceeded 2·5 seconds. Correspondingly, peak values of normalised derivatives were slightly lower in apex cardiograms recorded with displacement measuring devices, with the exception of pick-up no. 5, which showed also other significant aberrations. The average interval from the onset of the rise (point C) of the apex cardiogram to the peak of the derivative was significantly longer in apex cardiograms recorded with this device, because of inappropriate frequency characteristics.

Indeed, besides good frequency response at the low end of the spectrum the apex cardiographic system should also have good response characteristics in the high frequency range. Similarly, derivation of indices of contractility from left ventricular pressure data requires high-fidelity micromanometer recordings (Mason *et al.*, 1970; Mirsky *et al.*, 1972). Differences found in the present study between results of the 6 apex cardiographic transducer systems may be partially attributed to differences in application technique, but are probably a result of differences in response characteristics in the high frequency range.

Differences in technique of application of the 6 transducer systems were kept as minimal as possible. Such differences, however, are unavoidable, for example with respect to the exact place at the site of maximal impulse and the use of the same application pressure, as a result of the different pick-up diameters and sensing mechanisms.

Response characteristics of the 6 apex cardiographic transducers in the high frequency range were variable. In order to ensure maximal reproducibility of the normalised apex cardiographic derivative, linearity is needed, at least to 50 Hz, with some filtering to produce well-recognised alterations in roll-off features. Indeed, as a result of the thoracic wall resonance, high frequency heart sounds affect the apex cardiogram more than the left ventricular pressure curve. In addition, in unfiltered high-fidelity left ventricular pressure curves, notches corresponding to high frequency components of the first sound may cause spuriously large $(dP/dt)/P$ ratios.

CONCLUSION AND CLINICAL APPLICATIONS

In order to assure maximal reproducibility, technical characteristics of the recording device should be taken into account and an optimal recording technique be used. This has been underlined by several investigators with respect to the morphological features of the apex cardiogram (Kesteloot *et al.*, 1969; Willems, 1973). From the present study it is evident that the same holds true for measurements derived from its normalised derivative.

This conclusion should not be interpreted as a criticism of apex cardiography but should caution against an uncritical comparison of results obtained by authors using different devices.

Two important statements can be made as a result of our study. Firstly, the average differences between different transducers did not exceed 5 to 8 per cent. The mean difference in the peak amplitude of the normalised derivative obtained with the 6 different transducers was only 3·2 per cent. This was the best measurement with regards to reproducibility in the present investigation. These findings in the dog obtained under ideal circumstances, however, cannot be transferred to routine patient care. To these results one should compare the 8 and 11 per cent variation figures obtained by Motomura *et al.* (1973) and Denef *et al.* (1975) in human subjects. It has been shown that these figures are no limiting factor in discriminating patient groups with normal and abnormal myocardial function. Secondly, results of so many other techniques and measurements (as for example LVEDP, cardiac index, ejection fraction) vary even more significantly as emphasised by Spodick (1975). Variations in observer performance, including perception and interpretation, for other data, on which even critical decisions are made, can be so great that they should encourage us to use non-invasive objective measurements, such as derived from the apex cardiogram, echocardiography, or quantitative scintigraphy, and to refine these as much as possible.

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A severe complication of pulmonary vein angiography

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SUMMARY A pulmonary vein angiogram was performed using a pressure injection with the tip of an end and side hole catheter in a near-wedge position; extravasation of contrast material into a bronchus occurred, causing severe bronchoconstriction. It may be possible to avoid this complication by the use of an end hole balloon catheter in the wedge position, slow flow rates of contrast material, and low pressure injections.

Recent surgical advances for complex malformations involving infundibular or pulmonary valve or artery 'atresias' demand detailed knowledge of mediastinal pulmonary arteries. Recently, Singh (Rigby *et al.*, 1977; Singh *et al.*, 1978) and Nihill *et al.* (1978) have shown that pulmonary vein angiography can be used to visualise pulmonary artery segments not seen on anterograde cineangiograms. We employed the technique of Singh *et al.* and experienced a serious complication, the extravasation of contrast material into a bronchus. The patient developed severe respiratory embarrassment requiring intensive care treatment of pulmonary oedema.

Case report

An 11-year-old girl with severe cyanotic congenital heart disease has been followed at The Hospital for Sick Children, Toronto, since the age of 5 years. A Blalock-Hanlon septectomy was performed elsewhere when she was aged 3 years. When first seen at our institution, in 1972, cardiac catheterisation was interpreted to show double outlet right ventricle, ventricular septal defect, d-malposition of the great arteries, hypoplastic right ventricle, subvalvar and valvar pulmonary stenosis, and absent left pulmonary artery. She underwent a right Blalock-Taussig anastomosis at that time. Cyanosis increased during 1977, and in 1978 a further cardiac catheterisation showed also a straddling right atrioventricular valve and left juxtaposed atrial appendages.

Further operation was considered but the presence or absence of the left pulmonary artery was in doubt. In order to determine this, we undertook selective bronchial arteriography and left pulmonary vein angiography. The patient was sedated with an intramuscular combination of chlorpromazine, promethazine, and pethidine (Smith *et al.*, 1958). Intravenous doses of diazepam (10 mg) were given after percutaneous entry of the right femoral artery and vein. Selective bronchial artery injections failed to show a left pulmonary artery. A No. 7 Goodale-Lubin catheter was then advanced from the inferior vena cava, across the atrial septum, and into the left lower pulmonary vein. Atropine (0·04 mg) was administered intravenously. After general anaesthesia was induced with halothane and oxygen, the catheter was wedged in the vein and then withdrawn 1 to 1·5 cm. The pressure tracing no longer showed the wedge waveform. Twelve ml (0·3 ml/kg) of Hypaque 75 were injected at 20 ml/s. The pressure required for this volume and flow rate was 450 PSI. Much of the dye passed into other pulmonary veins and the left atrium. There was a large extravasation of contrast into the left lower lobe immediately after the injection. The contrast material entered the left lower lobe bronchus and then the left main bronchus (Fig.); the flow of contrast within the bronchus was predominantly toward the hilum. The patient developed increased cyanosis and severe bronchospasm; the anaesthetist noticed increased airway resistance to hand ventilation. Hydrocortisone sodium succinate (100 mg) was given intravenously, as well as another 0·04 mg atropine. The bronchospasm lasted approximately 10 minutes.

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[1] Supported by the Ontario Heart Foundation.

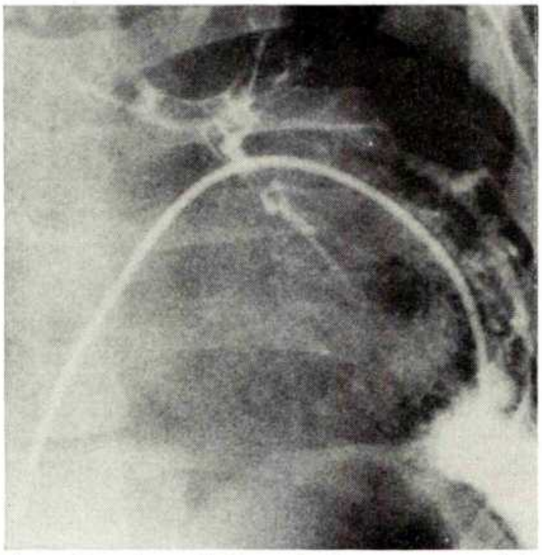

Fig. *Cineangiographic frame showing contrast material within the left main bronchus and the parenchymal stain.*

No mediastinal left pulmonary artery was seen. There was, however, a large residual stain in the left lower lobe. The patient was taken to the surgical recovery room immediately after stabilisation and subsequent chest *x*-ray films showed resolution of both the stain and local pulmonary oedema over the next 48 hours.

At operation on the third post-catheter day a central aortico-pulmonary anastomosis was performed. No left pulmonary artery was found at that time. The patient was discharged on the 12th postoperative day with improvement of her cyanosis.

Discussion

The technique used in this patient was that reported by Singh *et al.* (1978). They describe a pressure injection into an end hole or end and side hole catheter of 1 ml/kg of contrast material, with the catheter tip just short of the wedge position. They did not state the flow rate achieved. We used an end and side hole catheter (Goodale-Lubin) with a dose of contrast material of only 0·3 ml/kg. The pressure reached at the time of injection was 31·6 kg/cm^2 (450 PSI). In order to show that the catheter tip was not in the wedge position, we repeated the injection at a later time in our laboratory with the catheter tip in a bowl of saline. The pressure again was 31·6 kg/cm^2 (450 PSI). If the catheter had been in the wedge position during the catheterisation, it is likely that the pressure required would have been higher. We do not know what pressure is required to rupture pulmonary vessels and lead to an extravasation of contrast material into the airways.

The only complication mentioned by Singh *et al.* (1978) was the extravasation of contrast into the pulmonary parenchyma (stain) followed by transient pulmonary oedema. Nadas and Fyler (1972) did not discuss any complications whatsoever. Singh *et al.* (1978) reported a personal communication from W. Porstmann that extravasation of contrast was *essential* for proper visualisation of the pulmonary artery.

Differences in the technique of the injection have been reported. Takamiya *et al.* (1973) recommended a dose of 0·8 ml per kg of contrast material. Levin *et al.* (1978) described the injection of 12 to 15 ml of contrast material at a rate of 3 to 4 ml/s, with the catheter in the wedge position. No complications were discussed. Nihill *et al.* (1978) have the largest reported experience with pulmonary vein angiography. They used Goodale-Lubin or Ross catheters (end and side hole) in the wedge position. They recommended a dose of contrast material of 0·3 to 0·45 ml per kg, injected slowly (1 ml/s) by hand until visualisation of the pulmonary artery occurred. Then 1 to 2 ml per kg of flush solution were injected at 2 ml/s to enhance the filling of larger pulmonary artery branches. The complications included cough in all patients and one parenchymal extravasation with a small amount of contrast entering the bronchus. There were no ill-effects from this extravasation. They postulated that the extravasation occurred because of a too rapid rate of injection; our experience supports that hypothesis. They also stated that coughing was associated with extravasation in their patient. They did not describe the sedation used for catheterisation, but our use of general anaesthesia obliterated the cough reflex without preventing this complication.

We followed the recommendations of Singh *et al.* (1978) for the performance of a pulmonary vein angiogram in a patient with suspected left pulmonary artery atresia. Extravasation of contrast material into the left bronchus caused severe bronchoconstriction and respiratory embarrassment. We speculate that this severe complication was caused by the high pressure and flow dictated by the near wedge position of the catheter. The use of an end hole balloon catheter in the wedge position would permit low flow rates and low pressures and may prevent extravasation of contrast material during pulmonary vein angiography.

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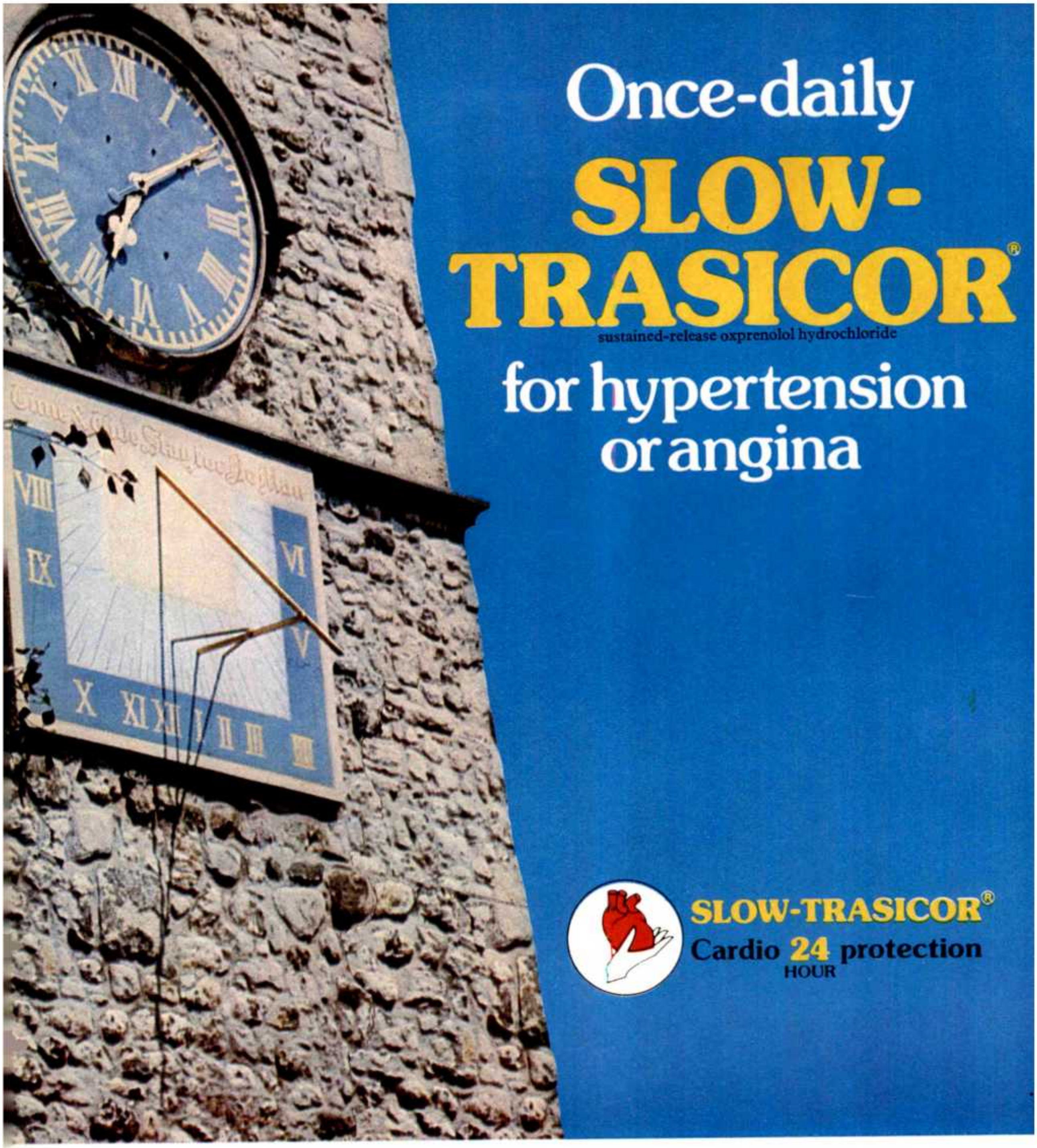

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British Heart Journal, 1979, **41**, 730-733

Mitral valve replacement for mitral stenosis caused by Libman-Sacks endocarditis

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SUMMARY A woman who developed mitral stenosis from Libman-Sacks endocarditis is described. The mitral valve was replaced by a Starr-Edwards prosthesis. One year later, despite her being maintained on steroids and azathioprine, the verrucous endocarditis progressed to cause sudden, severe dysfunction of the prosthetic valve.

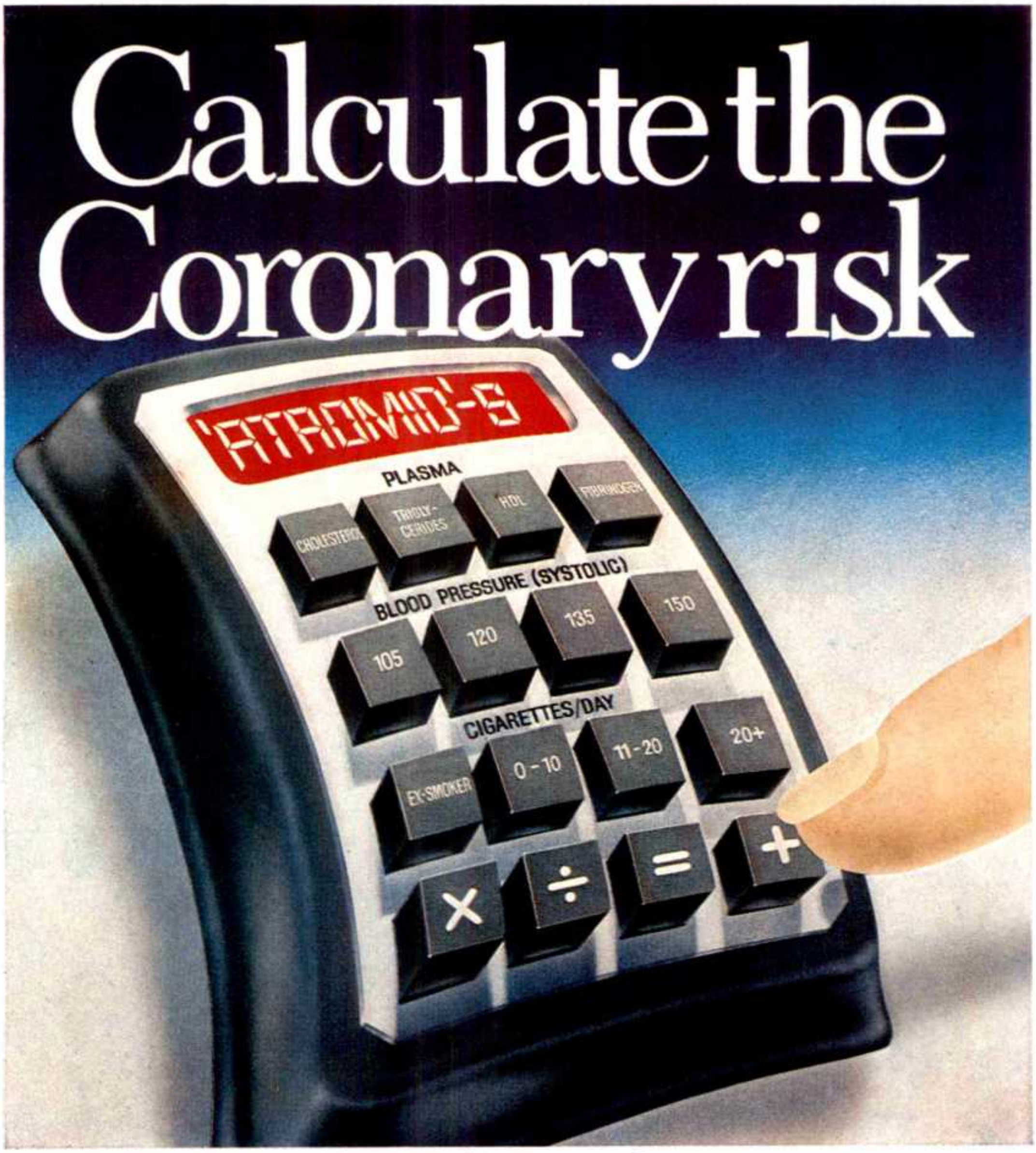
A non-bacterial verrucous endocarditis which was later shown to be associated with systemic lupus erythematosus was described by Libman and Sacks in 1924. Since then endocardial involvement found at necropsy in patients with systemic lupus erythematosus has been reported in 13 to 63 per cent of cases (Kong *et al.*, 1962; Heijtmancik *et al.*, 1964; Bulkley and Roberts, 1975a). Valvular involvement rarely produces significant haemodynamic dysfunction (Kong *et al.*, 1962; Heijtmancik *et al.*, 1964), and only 4 instances of valve replacement have been reported. Shulman and Christian (1969) described 3 patients with aortic regurgitation, 1 of whom required valve replacement and a further case was added by Oh *et al.* (1974). Mitral valve replacement has been described by Murray *et al.* (1975) and 1 has been reported from the National Institute of Health, Bethesda, Maryland (Myerowitz *et al.*, 1974; Paget *et al.*, 1975). We report a patient with systemic lupus erythematosus who presented with obstruction of the mitral valve and after mitral valve replacement proceeded to obstruction of the prosthesis within one year of operation. As far as we know, no case has been previously described in which active verrucous endocarditis has progressed to cause serious dysfunction of a prosthetic valve.

Case report

A 36-year-old housewife who had no past history of rheumatic fever was admitted in January 1975. For 5 months she had suffered from a febrile illness associated with myalgia and painful swollen knee and ankle joints. One month before admission she experienced 3 episodes of pleuritic chest pain. Two weeks later she noted shortness of breath on one flight of stairs and developed a dry cough, troublesome at night. On examination she was normotensive and in sinus rhythm. There were no signs of congestive cardiac failure. The pulmonary component of her second heart sound was loud and a short soft diastolic murmur was heard at the apex. The rest of her physical examination was normal. Investigations showed her haemoglobin to be 12·1 g/dl, white cell count 11 000/mm^3 with a normal differential, ESR 55 mm/h, blood urea 6 mmol/l. Antinuclear antibody was negative but lupus erythematosus cells were present. Blood cultures were consistently negative. Electrocardiogram showed sinus rhythm and left atrial hypertrophy. Echocardiography indicated mitral valve disease with thickening and rigidity of the valve cusps. The intracardiac pressures found at cardiac catheterisation were as follows: right atrium: mean 9 mmHg; right ventricle: 50/0-10 mmHg; pulmonary artery: 50/24 mmHg; pulmonary wedge pressure: mean 31 mmHg; left ventricle: 125/0-13 mmHg; aorta: 125/80 (mean 95) mmHg. A left ventricular angiogram showed a filling defect arising from the interventricular septum. This was thought to be either a thickened papillary muscle or vegetations associated with the mitral valve (Fig. 1).

A diagnosis of systemic lupus erythematosus was made and it was thought the patient had endocardial involvement affecting the mitral valve. The patient was treated with frusemide, prednisone 30 mg daily, and azathioprine 100 mg daily and her condition improved.

In March 1976 she was readmitted with increasing shortness of breath and ankle oedema. She was apyrexial. Her jugular venous pressure was raised 2 cm and she had fine crepitations at both bases. The apical diastolic murmur was still present. Electrocardiogram showed sinus rhythm and there was pulmonary venous congestion on the



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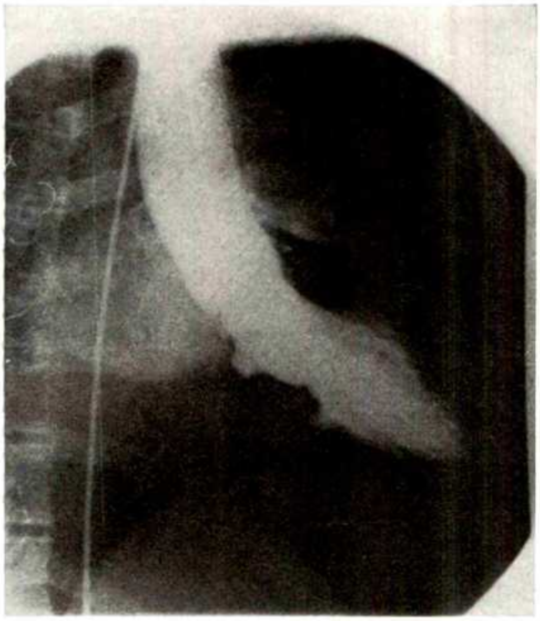

Fig. 1 *Left ventriculogram showing a filling defect which was thought to be vegetations associated with the mitral valve.*

chest *x*-ray film. Her haemoglobin was 10·3 g/dl, white cell count 12 000/mm^3, with a normal differential and ESR 74 mm/hour.

In view of her deteriorating clinical condition and the presence of mitral stenosis it was decided to explore her mitral valve. At operation the orifice of the mitral valve was almost completely obscured by a plaque of red granulation tissue resembling clot. A tiny aperture at the anterolateral commissure was the only communication to the left ventricle. The tissue extended onto the left atrial wall and measured 5 cm in diameter by 0·5 cm in thickness. It was so adherent to the valve cusp that it could not be separated. The valve was, therefore, excised with it and the affected left atrial wall was scraped clean. The valve was replaced by a No. 3M Model 6120 Starr-Edwards prosthesis without complication. There was no evidence of disease in the left ventricle.

Examination of the valve showed it to be thickened and fibrotic with increased vascularity. A large fibrinous vegetation was attached to its upper surface. Areas of fibrinoid degeneration were present within the valve and the histological appearances were considered to be consistent with the diagnosis of Libman-Sacks endocarditis. No infective agent was found (Fig. 2).

The patient made an uncomplicated recovery and was discharged on prednisone 10 mg daily, azathioprine 100 mg daily, warfarin, and frusemide.

She remained well on the above regimen until January 1977 when she developed more discomfort and swelling in the knees and ankles and her ESR was found to have risen from 42 to 62 mm/hour. Prednisone was increased to 15 mg daily. In February 1977 she was readmitted as an emergency with a 3-day history of increasing shortness of breath, haemoptysis, and paroxysmal nocturnal dyspnoea. On examination she was cold and clammy. Her pulse rate was 100 per minute, blood pressure 90/60 mmHg, and there were signs of severe pulmonary oedema. A loud pansystolic murmur was heard at the apex and radiated to the axilla. It was thought she had developed acute mitral regurgitation with resultant cardiac failure. Her condition deteriorated rapidly after admission and she had a cardiac arrest. She was immediately resuscitated, taken to theatre and put on cardiopulmonary bypass. At operation the ball of the mitral prosthesis was found to be fixed in the open position. Three-quarters of the orifice below the valve seating was obstructed by friable, acellular tissue leaving a small fixed opening which was both obstructive and regurgitant. When the prosthesis was removed the left ventricular cavity was found to contain a large mass of similar tissue attached to the posterior wall. This was removed with the prosthesis and a new No. 4M Model 6120 Starr-Edwards valve was inserted.

Postoperatively the patient remained critically ill. She was unconscious, unresponsive, and developed epileptic fits. She became anuric and required peritoneal dialysis. In spite of all supportive measures her condition deteriorated and she died 4 days later.

Histological examination of the tissue removed from around the prosthetic valve showed it to consist predominately of collagen, areas of which were necrotic. It was relatively acellular but occasional plasma cells were present. On the surface were both organised and unorganised thrombus. Necropsy showed severe bilateral pulmonary oedema and hepatic venous congestion. There was a right-sided cerebral infarction. Both kidneys showed the gross appearances of acute tubular necrosis and on histological examination the characteristic lesions of systemic lupus erythematosus were seen.

Discussion

The initial diagnosis of systemic lupus erythematosus in this patient was made on the history of arthritis without deformity. the evidence of pleural involvement, a raised sedimentation rate, and the presence of lupus erythematosus cells. When a

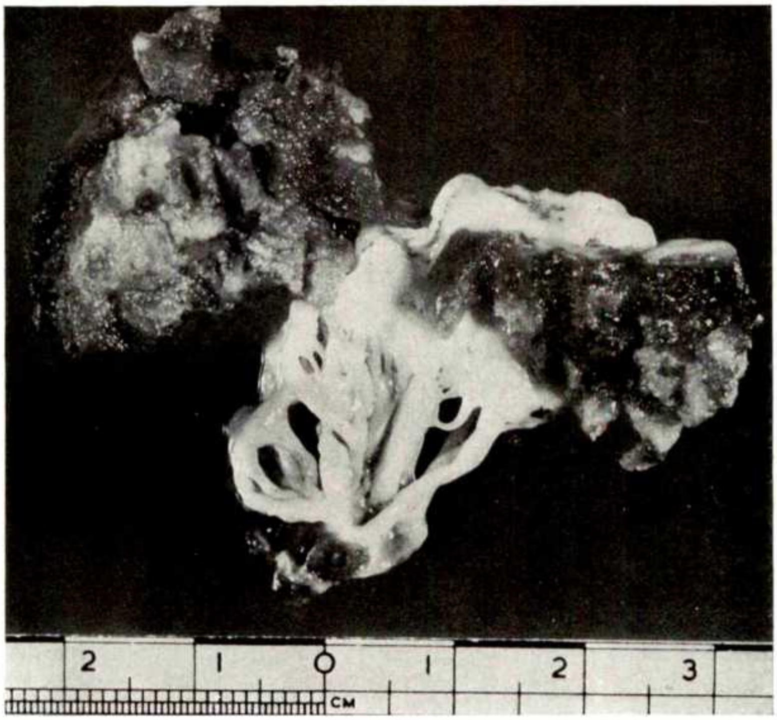

Fig. 2 *Excised mitral valve with adherent vegetations.*

diastolic murmur at the apex was heard the possibility of Libman-Sacks endocarditis was raised. A murmur is the commonest initial cardiovascular manifestation (Kong *et al.*, 1962). There is, however, a poor correlation between the appearance of a murmur and the presence of Libman-Sacks valvulitis at necropsy (Shearn, 1959; Kong *et al.*, 1962). Mitral valve involvement was demonstrated in this case by echocardiography and cardiac catheterisation.

The left ventricular filling defect seen at cardiac catheterisation (Fig. 1) was thought to be a mass of verrucous material associated with the mitral valve. A similar appearance has been reported by Seningen *et al.* (1974). At the initial operation, however, no mass was seen and the left ventricle was grossly free of disease. At the second operation a large mass of tissue was found attached to the posterior wall of the left ventricle and this was the cause of the prosthetic valve dysfunction.

The pathology of the endocarditis has been well described (Gross, 1940; Klemperer *et al.*, 1941). Histological examination of the tissue removed from this patient did not show all the classical features but the absence of lupus erythematosus cells and haematoxyphil bodies has been reported in other cases (Oh *et al.*, 1974) and was attributed to the effect of steroid therapy. Recently Bulkley and Roberts (1975a) have also drawn attention to the alteration to pathology induced by corticosteroid therapy. They postulate that 'healing' of Libman-Sacks endocarditis may occur by fibrosis and calcification. This was rare before the advent of steroids but now, either as a direct effect of the drug or as a result of increased longevity of the patients, this 'healing' process is seen more commonly. One consequence of this could be to increase the incidence of valve dysfunction by scarring (Bulkley and Roberts, 1975a).

The distribution of the endocardial lesions also has been modified by steroid therapy. Previously all four valves were commonly involved but now there is a preponderance of left-sided lesions affecting particularly the mitral valve (Heijtmancik *et al.*, 1964; Bulkley and Roberts, 1975b). In the two previously reported cases of mitral valve replacement in this condition the lesions had produced mitral regurgitation. It is of interest that in this patient the vegetations produced predominant mitral stenosis.

Our patient had an initially successful mitral valve replacement but over the course of a year the endocarditis progressed to produce malfunction of the prosthesis, which was ultimately fatal. During this period therapy with prednisone and azathioprine was maintained and though her sedimentation rate had remained moderately raised at about 42 mm/hour she had been asymptomatic. One month before her final admission she developed a recurrence of joint pains and the dose of prednisone was increased. Perhaps, in spite of being asymptomatic, the therapy was inadequate and she should have been on higher doses. However, Heijtmancik *et al.* (1964) question the value of steroids in preventing Libman-Sacks endocarditis and the history of this patient may provide further evidence to support this view.

We, therefore, offer a warning that the endocardial manifestations of the disease can progress despite therapy, and relatively silently, to cause sudden and severe dysfunction of a prosthetic valve. In addition, we feel that the disease behaves like a malignant growth with local extensions, and perhaps the affected portion of left atrial wall, found at the initial operation, should have been excised.

We thank Dr F. Scadding for referring this patient.

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British Heart Journal, 1979, **41**, 734-737

Alternating atrial and ventricular tachycardia[1]

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SUMMARY A patient with alternating atrial and ventricular tachycardia is described. He had an acute myocardial infarction and was taking digitalis. The atrial tachycardia, which was occasionally associated with aberrant ventricular conduction, was able to interrupt the ventricular tachycardia though the reverse was not true, suggesting a retrograde conduction block. This patient shows that atrial and ventricular arrhythmias can alternate and, since tachycardia with aberrant ventricular conduction can closely resemble ventricular tachycardia, intra-atrial electrocardiography may be necessary to establish an accurate diagnosis.

Simultaneous or double tachycardias are uncommon arrhythmias. Simultaneous atrial and atrioventricular junction tachycardia has been previously reported and is thought to be associated with digitalis toxicity (Wishner *et al.*, 1972). In addition, simultaneous atrial and ventricular tachycardia has been observed (Katz and Pick, 1956; Halkin and Kaplinsky, 1971; Puech, 1975). Distinguished from a double tachycardia is an alternating tachycardia in which two separate arrhythmias alternate in control of the ventricles. No previous mention of this entity in a 30-year review of the world reports on tachycardia including major textbooks of electrocardiography (Katz and Pick, 1956; Corday and Irving, 1961; Dreifus *et al.*, 1966; Sandoe *et al.*, 1970; Bellet, 1971; Chung, 1971; Puech, 1975) suggests that such an arrhythmia is rarely recognised. Reported here is a patient who had alternating atrial and ventricular tachycardia in the course of a recent myocardial infarction, mild congestive heart failure, and possible digitalis intoxication.

Case report

A 57-year-old Caucasian man was admitted to the coronary care unit with a 2-day history of chest pain. An electrocardiogram showed an acute inferolateral and posterior myocardial infarction with normal sinus rhythm. Two days after admission the patient developed râles bilaterally. A chest *x*-ray film showed pulmonary vascular congestion with slight cardiac enlargement. The patient was treated with 0·5 mg digoxin followed by an additional 0·25 mg in 8 hours. Two hours after the last dose of digoxin an arrhythmia developed, which by intra-atrial electrocardiography was shown to be episodes of atrial tachycardia with a rate of 180 per minute and aberrant ventricular conduction in the initial few beats (Fig. 1). Spontaneous conversion to sinus rhythm occurred. One hour later a tachyarrhythmia again developed with a broad QRS configuration similar to the pattern of the aberrant ventricular complexes seen intermittently with the previous atrial tachycardia. The new arrhythmia had a slower rate (150 beats/minute), with occasional fusion beats and alternated with episodes of atrial tachycardia at a rate of 180 per minute (Fig. 2, top). Intra-atrial electrocardiography revealed the rhythm to be ventricular tachycardia which was terminated by a short burst of atrial tachycardia. This latter arrhythmia converted spontaneously to sinus rhythm (Fig. 2, bottom). A pattern of alternating atrial and ventricular tachycardia was then seen (Fig. 3). At no time did the ventricular rhythm interrupt the atrial tachycardia, and it resumed when the atrial tachycardia stopped. Both rhythms were successfully ablated with intravenous lignocaine.

Discussion

The alternating nature of these arrhythmias and the demonstration of the related unidirectional interference are unique. Both would have been more difficult to recognise without the use of intra-atrial electrocardiography. The use of this technique for the diagnosis of cardiac arrhythmias has been emphasised previously (Goldreyer, 1972).

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[1] Grant support in part by Portland VAH MRIS.

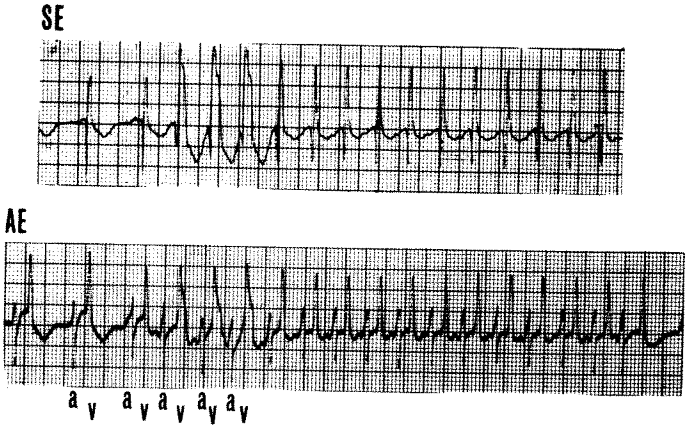

Fig. 1 *Simultaneous surface electrocardiogram (SE) and atrial electrocardiogram (AE). The surface electrocardiogram was recorded from the cardiac monitor and shows 3 wide QRS complexes at the onset of atrial tachycardia. The simultaneously recorded atrial electrocardiogram shows that the wide QRS pattern is a result of aberrant ventricular conduction, as each is preceded by an atrial depolarisation. The surface electrocardiogram and the atrial electrocardiogram were obtained from separate recorders and mounted such that corresponding complexes coincided. Recording speed was 25 mm/s. a, atrial depolarisation, v, ventricular depolarisation.*

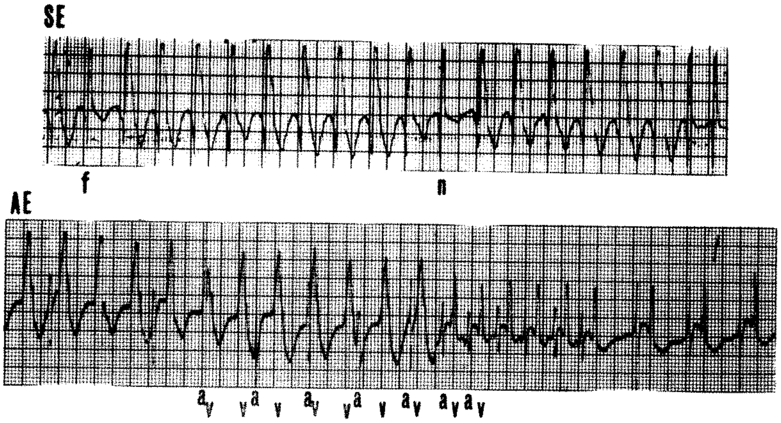

Fig. 2 *Non-simultaneous surface electricardiogram (SE) and atrial electrocardiogram (AE). The surface electrocardiogram (monitor lead position unchanged from Fig. 1) shows a broad QRS pattern resembling the QRS configuration of the aberrantly conducted ventricular complexes with the previous atrial tachycardia (see Fig. 1). A fusion beat (f) and a normal complex (n) are present. Two beats of atrial tachycardia are seen at the end of the tracing. A non-simultaneous atrial electrocardiogram (AE) shows atrioventricular dissociation and ventricular tachycardia. Ventricular tachycardia ends with a short run of atrial tachycardia before conversion to sinus rhythm. Recording speed was 25 mm/s.*

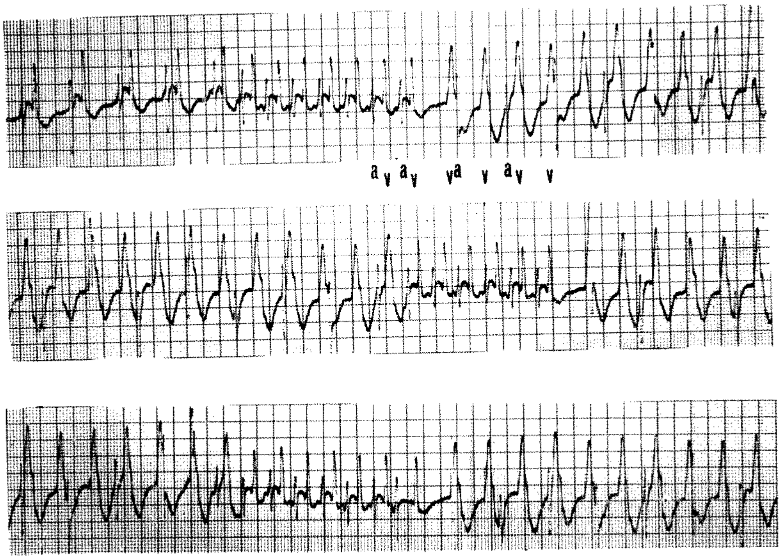

Fig. 3 *A continuous intra-atrial recording of alternating atrial and ventricular tachycardia which is initiated by sinus rhythm. Sinus rhythm with a rate identical to that at the beginning of the tracing is seen during ventricular tachycardia. Recording speed was 25 mm/s.*

The first surface tracing was confusing because a wide QRS pattern was seen intermittently with what appeared to be a paroxysmal atrial tachycardia. The atrial electrocardiogram showed that the wide QRS pattern was a result of aberrant ventricular conduction (Fig. 1). The second rhythm disturbance could have been assumed to be paroxysmal atrial tachycardia with aberrant ventricular conduction at a slightly slower rate; however, the atrial electrocardiogram showed that there was dissociation between the atria and ventricles (Fig. 2).

It is interesting to note that anterograde conduction allowed the atrial arrhythmia with the more rapid rate to 'overdrive' and suppress the ventricular tachycardia. At no time did the ventricular arrhythmia interrupt the atrial arrhythmia or affect the atrial firing rate indicating a block of retrograde conduction. Though the genesis of this rhythm disturbance remains speculative, recent work suggests that most atrial and ventricular arrhythmias are due to re-entrant mechanisms (Coumel and Barold, 1975). One or both arrhythmias, however, could have originated from isolated ectopic foci.

The simultaneous occurrence of two tachycardias has been well documented (Wishner *et al.*, 1972). The unequivocal demonstration of separate arrhythmogenic foci during a junctional or ventricular tachycardia, however, has not been apparent in all cases (Bernstein *et al.*, 1952; Halkin and Kaplinsky, 1971). It is possible that some previously reported simultaneous tachycardias were actually alternating tachycardias. Though different mechanisms could be responsible for alternating and simultaneous tachycardias, both rhythm disturbances appear to be equally serious and occur during similar clinical circumstances.

These arrhythmias occurred in the clinical setting of a recent myocardial infarction, mild congestive heart failure, and digitalis therapy. Ventricular tachycardia is not uncommonly associated with myocardial infarction; however, atrial tachycardia is unusual in this setting, and, when present, is frequently seen among patients receiving digitalis (DeSanctis *et al.*, 1972). There was no evidence for an atrial infarction on the admission electrocardiogram or post-arrhythmia electrocardiogram arguing against this as an aetiology for our patient's atrial tachycardia.

Atrial tachycardia with aberrant ventricular conduction can closely resemble ventricular tachycardia and, as seen in this case, both arrhythmias can occur together. Atrial electrocardiography may be necessary to establish an accurate diagnosis and to select the proper treatment modality.

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Obituary

British Heart Journal, 1979, **41**, 738-739

Arthur Morgan Jones

Dr Arthur Morgan Jones died on 3 January 1979 in the Manchester Royal Infirmary.

A native of Glamorgan, Arthur Morgan Jones was educated in Bangor, North Wales, and entered the University of Manchester as a Dalton Scholar in physiology in 1929. He took a first class honours degree in physiology in 1934 and followed this with an MSc in 1935. He graduated MB ChB with honours in 1938. He took the membership of the Royal College of Physicians in London in 1942 and was elected to the fellowship in 1948.

Morgan Jones' undergraduate career was distinguished by prizes and scholarships in physiology, medicine, and pharmacology. After graduation he joined the late Professor Bramwell's unit as house physician thus beginning what was to be a long and fruitful partnership. After a period in research in the University of Cambridge he returned to be RMO at the Manchester Royal Infirmary and his success in this post is still legendary. After this his appointment as consultant physician to the Manchester Royal Infirmary in 1948 was assured. In 1946-47 he worked in the United States holding first of all a Leverhulme Research Scholarship from the Royal College of Physicians and later a Rockefeller Travelling Fellowship. This work was mainly in Cleveland in Harold Feil's department and it was a period which he enjoyed very much. He remained thereafter a frequent visitor to the United States. He succeeded Professor Bramwell as director of the Department of Cardiology at the Manchester Royal Infirmary on the latter's retirement in 1954, and he remained director until his own retirement in 1971. He was reader in cardiology in the University of Manchester and president of the Manchester Medical Society in

1969-70. He was an enthusiastic member of the British Cardiac Society, serving on Council in 1954-58 and again in 1959-60. He was a founder member of Council of the British Heart Foundation and also on the Research Committee of the International Society of Cardiology in 1961-66.

Morgan Jones' influence on cardiology in Manchester was profound and it was his collaboration with the late Professor Bramwell which led to the founding of the University Department of Cardiology at the Manchester Royal Infirmary. During the period 1936-47 he worked in basic physiology with the late Professor Walter Schlapp and also published several papers on clinical cardiology with Bramwell and with F. A. Langley. It was during this period that he first began to develop an interest in heart disease in pregnancy, his first paper on this topic being published in the *Postgraduate Medical Journal* in 1944. While in the United States he worked principally on the effect of posture on normal and abnormal cardiograms. Subsequently he developed and extended his interest in heart disease and pregnancy, publishing his classic book on the subject in 1951. In the 1950's he became increasingly interested in coronary disease and with Snow and Daber he was the first to show that sudden death was frequently not associated with demonstrable occlusion or infarction, a statement then which flouted current thinking but now has been thoroughly vindicated. His contributions to the field of coronary disease were recognised when he was invited to give the Strickland Goodall Memorial Lecture in 1969.

In addition to his original work he also found time to edit *Progress in Cardiology* and later *Modern Trends in Cardiology*, both successful books.

Although Morgan Jones' contribution to medicine and cardiology will not be forgotten quickly, he will be remembered best as a highly valued friend and colleague. In character he was kind, unpretentious, and totally honest. Those of us who worked with him and enjoyed his friendship were privileged indeed. He was not married.

E. GEOFFREY WADE

Correspondence

British Heart Journal, 1979, **41**, 740

Severe complication of pulmonary vein angiography

Sir,

We suggest that the complication described by Alpert and Culham on p. 727 of this issue can be avoided by a less wedged position of the catheter tip than that evidently used in this instance, and that a preliminary hand injection to check the suitability of the position is advisable. Extravasation is certainly not an essential for flow into the pulmonary arteries to occur and we aim to avoid it. While low pressures can sometimes produce the desired result, it is our experience that a pressure injection is more likely to give demonstration of the more central parts of the pulmonary arterial tree. It is important to withdraw the catheter immediately the injection is completed.

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AUTHOR INDEX

1979, Volume 41

ABE, H., *see* Hori, M. *et al.*
Matsuo, M. *et al.*
ABRAMS, L. D., *see* Silove, E. D. *et al.*
ADAMS, L., *see* Stephens, J. D. *et al.*
ADAMS, P. R. V., *see* Anderson, K. R. *et al.*
ADESANYA, C. O., *see* Sanderson, J. E. *et al.*
ADGEY, A. A. J., *see* Campbell, N. P. S. *et al.*
AHMAD, M. (& Hallidie-Smith, K. A.). Assessment of left-to-right shunt and left ventricular function in isolated ventricular septal defect. Echocardiographic study. 147
— *see also* Thompson, R. *et al.*
AHMAD, R., *see* Rajah, S. M. *et al.*
AHUMADA, G. G. (& Karlsberg, R. P., Jaffe, A. S., Ambos, H. D., Sobel, B. E., Roberts, R.). Reduction of early ventricular arrhythmia by acebutolol in patients with acute myocardial infarction. 654
ALLWORK, S. P. (& Anderson, R. H.). Developmental anatomy of the membranous part of the ventricular septum in the human heart, 275
ALPERT, B. S. (& Culham, J. A. G.). A severe complication of pulmonary vein angiography: case report. 727
AMBOS, H. D., *see* Ahumada, G. G. *et al.*
ANDERSON, K. R. (& Adams, P. R. V., Anderson, R. H.). Development of inlet zone of right ventricle in man. 362, *P.*
— (& Ho, S. Y., Anderson, R. H.). Location and vascular supply of sinus node in human heart. 28
ANDERSON, R. H., *see* Allwork, S. P. & Anderson, R. H.
Anderson, K. R. *et al.*
Crupi, G. *et al.*
Ho, S. Y. & Anderson, R. H.
Tynan, M. J. *et al.*
Zuberbuhler, J. R. & Anderson, R. H.
ANJORIN, F. I., *see* Sanderson, J. E. *et al.*
ANSON, R. CANEPA-, *see* Canepa-Anson, R.
ARONOW, W. S., *see* Chandraratna, P. A. N. *et al.*
ASTLEY, R., *see* Silove, E. D. *et al.*
Singh, S. P. & Astley, R.
ÅSTRÖM, H. (& Holmgren, A., Jonsson, B.). Blood volume in angina pectoris. 477
ATKINSON, L., *see* Bergman, G. W. *et al.*
Rothman, M. *et al.*
ATLAN, H., *see* Corne, R. A. *et al.*
AUMONT, M. C., *see* Merillon, J. P. *et al.*

BABER, N. S. Multicentre propranolol post-infarction trial. 365, *P.*
BAIN, W. H., *see* Taylor, K. M. *et al.*
BALASUBRAMANIAN, V. Systolic time intervals and impedance cardiography: correspondence. 254
— *see also* Mann, S. *et al.*
BALCON, R., *see* Brooks, N. *et al.*
BANIM, S. O., *see* Stephens, J. D. *et al.*
BARLOW, J. B., *see* McLaren, M. J. *et al.*
BARON, D. W. (& Poole-Wilson, P. A., Rickards, A. F.). 12-lead maximal exercise testing as a predictor of severe coronary artery disease. 364, *P.*
— *see also* Rickards, A. F. *et al.*
BECKER, A. E., *see* Caruso, G. & Becker, A. E.
Tynan, M. J. *et al.*
BENNETT, G. (& Canepa-Anson, R., Bourdillon, P. D. V., Yacoub, M. H., Ross, D. N.). Risks and results of reoperation for coronary artery disease. 370, *P.*
BENTALL, H. H. (& Rowland, E., Krikler, D. M.). Endocardial mapping and cryosurgery for arrhythmias. 371, *P.*
BERGMAN, G., *see* Rothman, M. *et al.*
BERGMAN, G. W. (& Atkinson, L., Jackson, G., Jewitt, D. E.). Changes in regional myocardial lactate metabolism after coronary bypass surgery. 369, *P.*
BERMAN, W., *see* Kinney, E. *et al.*
BESSENT, R. G., *see* Murray, R. G. *et al.*
BHATIA, M. L., *see* Kasturi, T. E. *et al.*
BINKHORST, R. A., *see* Van Herwaarden, C. L. A. *et al.*
BLOCK, P. C., *see* Johnson, R. A. *et al.*
BORDALO, A., *see* Waleffe, A. *et al.*
BOUCHER, C. A. (& Fallon, J. T., Johnson, R. A., Yurchak, P. M.). Cardiomyopathic syndrome caused by coronary artery disease. III: Prospective clinicopathological study of its prevalence among patients with clinically unexplained chronic heart failure. 613
BOURDILLON, P. D. V. (& Foale, R. A., Rickards, A. F.). Identification of atrial septal defects by cross-sectional contrast echocardiography. 382, *P.*
— *see also* Bennett, G. *et al.*
Foale, R. A. *et al.*
Poole-Wilson, P. A. *et al.*
BOYD, M. J., *see* Mather, H. M. *et al.*
BRAIMBRIDGE, M. V., *see* Shiu, M. F. *et al.*
BRANNAN, J. J., *see* Taylor, K. M. *et al.*
BREVETTI, G. (& Chiariello, M., Lavecchia, G., Rengo, F.). Effects of propranolol in a case of orthostatic hypotension: case report. 245
BRITISH CARDIAC SOCIETY. Autumn Meeting, London, November 1978, proceedings. 360
BRITTON, K. E., *see* Dymond, D. S. *et al.*
BROOKS, N. (& Cattell, M., Balcon, R., Honey, M., Sturridge, M., Wright, J.). Reoperation for recurrent angina. 369, *P.*
— (& Leech, G., Leatham, A.). Complete bundle-branch block. 637
BROWN, D., *see* Hall, R. J. C. *et al.*
BROWN, D. J., *see* Gibson, D. G. & Brown, D. J.
Gibson, D. G. *et al.*
BRUNINX, P., *see* Waleffe, A. *et al.*
BRUNT, J. N. H. (& Taylor, C. J., Rowlands, D. J.). Automated system to encourage more widespread use of quantitative ventriculography. 373, *P.*

CAMBRIDGE, G. (& Macarthur, C. G. C. M., Waterson, A. P., Goodwin, J. F., Oakley, C. M.). Antibodies to Coxsackie B viruses in congestive cardiomyopathy. 692
CAMM, A. J. (& Dymond, D., Spurrell, R. A. J.). Sinus node dysfunction associated with absence of right superior vena cava: case report. 504
— *see also* Wang, R. *et al.*

Campbell, I. W., *see* Hume, L. *et al.*

Campbell, N. P. S. (& Zaidi, S. A., Adgey, A. A. J., Patterson, G. C., Pantridge, J. F.). Observations on haemodynamic effects of mexiletine. 182

Canepa-Anson, R. (& Emanuel, R. W.). Elective aortic and mitral valve surgery in patients over 70 years of age. 493

— *see also* Bennett, G. *et al.*
  Rickards, A. F. *et al.*

Carmichael, D. J. S., *see* Vecht, R. J. *et al.*

Carruthers, M., *see* Taggart, P. *et al.*

Caruso, G. (& Becker, A. E.). How to determine atrial situs? 559

Casals, J., *see* Taylor, K. M. *et al.*

Cate, F. J. Ten, *see* Ten Cate, F. J.

Cattell, M., *see* Brooks, N. *et al.*

Caves, P. K., *see* Sang, C. T. M. *et al.*

Chakrabarti, R., *see* Meade, T. W. *et al.*

Chandraratna, P. A. N. (& Langevin, E., Langevin, J.). Pulsus alternans induced by glyceryl trinitrate paste in a patient with alcoholic cardiomyopathy: case report. 354

— (& Vlahovich, G., Aronow, W. S.). Echocardiographic study of significance of left ventricular minor axis shortening during pre-ejection phase of systole. 392

Chang, V. P., *see* O'Rourke, M. F. *et al.*

Chen, W. (& Gibson, D.). Relation of isovolumic relaxation to left ventricular wall movement in man. 377, *P.*

Chetty, S., *see* McKenna, W. J. *et al.*

Chiariello, M., *see* Brevetti, G. *et al.*

Chuaqui, B. Doerr's theory of morphogenesis of arterial transposition in light of recent research. 481

Chuquimia, R., *see* Vasquez, M. *et al.*

Citron, P., *see* Sutton, R. & Citron, P.

Clarke, B. F., *see* Hume, L. *et al.*

Clarke, D. B., *see* Silove, E. D. *et al.*

Clarke, S. E., *see* Hall, R. J. C. *et al.*

Coleman, E. N., *see* Houston, A. B. *et al.*

Coltart, D. J., *see* Shiu, M. F. *et al.*

Cooke, R. W. I. (& Pickering, D.). Poor response to oral indomethacin therapy for persistent ductus arteriosus in very low birthweight infants. 301

Corne, R. A. (& Gotsman, M. S., Weiss, A., Enlander, D., Samuels, L. D., Salomon, J. A., Warshaw, B., Atlan, H.). Thallium-201 scintigraphy in diagnosis of coronary stenosis. 575

Coto, E. O. (& Wilkinson, J. L., Dickinson, D. F., Rufilanchas, J. J., Márquez, J.). Gross distortion of atrioventricular and ventriculo-arterial relations associated with left juxtaposition of atrial appendages. *Bizarre form of atrioventricular criss-cross.* 486

Cotter, L. (& Miller, H. C.). Clinical and haemodynamic evaluation of mounted porcine heterograft in mitral position. 412

Craig, A., *see* Maddison, A. *et al.*

Craig, M. M., *see* Mann, S. *et al.*

Craige, E., *see* Mills, P. *et al.*

Cristal, N. (& Peterburg, I., Inbar-Yanai, I.). Atrial infarction leading to rupture: case report. 350

Crowther, A., *see* Shiu, M. F. *et al.*

Crupi, G. (& Anderson, R. H., Lincoln, C.). Complete transposition of great arteries with intact ventricular septum and left ventricular outflow tract obstruction: surgical management and anatomical considerations. 366, *P.*

Cueni, T. A., *see* Wainwright, R. J. *et al.*

Culham, J. A. G., *see* Alpert, B. S. & Culham, J. A. G.

Cumming, G. R. Maximal supine exercise haemodynamics after open heart surgery for Fallot's tetralogy. 683

Cummins, P., *see* Evemy, K. L. *et al.*

Currey, P. V. L., *see* Pitcher, D. W. *et al.*

Daneshwar, A. (& Tavakoli, D., Nazarian, J.). Marfanoid hypermobility syndrome associated with coarctation of the aorta: case report. 621

Daniels, O. Echocardiographic identification of aorta and main pulmonary artery in complete transposition: correspondence. 631

Davids, H. A., *see* Van Der Laarse, A. *et al.*

Davies, A. B. (& Foale, R. A., Rickards, A. F.). Cross-sectional echocardiographic assessment of aortic valvar stenosis. 374, *P.*

Davies, G. J. (& Fakhrai, B., Morgan, A., Muir, J. R.). Estimation of myocardial infarct size in man using 99mTc polyphosphate. 668

Davies, M., *see* Mills, P. *et al.*

Davies, R. (& Pickering, T. G., Morganti, A., Wilson, M., Laragh, J. H.). Blockade of cardiac and renal beta-receptors by low dose propranolol in normal subjects. *Clues to its antihypertensive effect.* 331

Davis, A., *see* Mills, P. *et al.*

Davison, K. G., *see* Sang, C. T. M. *et al.*

Dawson, R., *see* Rowland, E. *et al.*

De Geest, H., *see* Willems, J. L. H. *et al.*

De Leval, M., *see* McNicholas, K. *et al.*
  O'Riordan, J. *et al.*

De Swiet, M. (& Fayers, P., Shinebourne, E. A.). Epidemiological study of blood pressure in infancy. 383, *P.*

Denef, B., *see* Willems, J. L. H. *et al.*

Der Schoot, J. Van, *see* van der Schoot, J.

Di Eusanio, G. (& Ray, S. C., Donnelly, R. J., Hamilton, D. I.). Open heart surgery in first year of life using profound hypothermia (core cooling) and circulatory arrest *Experience with 134 consecutive cases.* 294

Dickinson, D. F. (& Houlsby, W. T., Wilkinson, J. L.) Unusual angiographic appearances of the left ventricle in 2 cases of Pompe's disease (glycogenosis type II). 238

— *see also* Coto, E. O. *et al.*

Dimock, F. R., *see* Falk, R. H. *et al.*

Doi, Y. (& McKenna, W., Gehrke, J., Goodwin, J. F.). Diagnosis of obstructive and non-obstructive hypertrophic cardiomyopathy: is echocardiography of value? 379, *P.*

Donaldson, R., *see* Taggart, P. *et al.*

Donnelly, R. J., *see* Di Eusanio, G. *et al.*
  Hamilton, D. I. *et al.*

Dorp, W. G. Van, *see* Van Dorp, W. G.

Dr Heinz Karger Prize. Notice. 128

Dubrow, I. W., *see* Thanopoulos, B. D. *et al.*

Dunning, A. J., *see* Krediet, R. T. & Dunning, A. J.

Durrer, D., *see* Wackers, F. J. Th. *et al.*

Dymond, D. S. (& Jarritt, P. H., Britton, K. E., Spurrell, R. A. J.). Detection of postinfarction left ventricular aneurysms by first pass radionuclide ventriculography using a multicrystal gamma camera. 68

— (& Stone, D. L., Elliott, A. T., Britton, K. E., Spurrell, R. A. J.). Biplane first pass radionuclide ventriculography in assessment of wall motion abnormalities in patients with acute myocardial infarction. 378, *P.*

— *see also* Camm, A. J. *et al.*
  Stephens, J. D. *et al.*

Ead, H., *see* Stephens, J. D. *et al.*

Effert, S., *see* Hagemann, K. *et al.*

Elliott, A. T., *see* Dymond, D. S. *et al.*

Emanuel, R. W., *see* Canepa-Anson, R. & Emanuel, R. W.

Enlander, D., *see* Corne, R. A. *et al.*

Epstein, S. E., *see* Maron, B. J. *et al.*

Essen, R. V., *see* Hagemann, K. *et al.*

Eusanio, G. Di, *see* Di Eusanio, G.

Evemy, K. L. (& Cummins, P., Littler, W. A.). Effects of long-term beta-adrenoreceptor blockade in rabbits. 383, *P.*
Ewing, D. J., *see* Hume, L. *et al.*

Fakhrai, B., *see* Davies, G. J. *et al.*
Falk, R. H. (& Dimock, F. R., Sharkey, J.). Prosthetic valve endocarditis resulting from *Nocardia asteroides*: case report. 125
Fallon, J. T., *see* Boucher, C. A. *et al.*
Fayers, P., *see* de Swiet, M. *et al.*
Fennis, J. F. M., *see* van Herwaarden, C. L. A. *et al.*
Fieller, N. R. J., *see* Martin, M. A. & Fieller, N. R. J.
Figueras, J. (& Taylor, W. R., Ogawa, T., Forrester, J. S., Singh, B. N., Swan, H. J. C.). Comparative haemodynamic and peripheral vasodilator effects of oral and chewable isosorbide dinitrate in patients with refractory congestive cardiac failure. 317
Fisher, E. A., *see* Thanopoulos, B. D. *et al.*
Flameng, W., *see* Sesto, M. *et al.*
Flamm, M. D., *see* McHenry, M. M. *et al.*
Fleming, H. A. Sarcoid heart disease in United Kingdom. 379, *P.*
Foale, R. A. (& Bourdillon, P. D. V., Somerville, J., Rickards, A. F.). Echocardiographic features of anomalous systemic and coronary venous return. 381, *P.*
— *see also* Bourdillon, P. D. V. *et al.*
  Davies, A. B. *et al.*
  Poole-Wilson, P. A. *et al.*
Forrester, J. S., *see* Figueras, J. *et al.*
Forse, G., *see* Oakley, D. *et al.*
Fox, K. M. Relation between praecordial projection of ST segment changes after exercise and coronary angiography. 361, *P.*
— (& Selwyn, A., Shillingford, J. P.). Objective non-invasive assessment of coronary artery bypass graft surgery. 368, *P.*
— *see also* Selwyn, A. P. *et al.*
Friedli, B., *see* Oberhänsli, I. & Friedli, B.
Fukui, S., *see* Hori, M. *et al.*
Furman, S., *see* Mehra, R. & Furman, S.

Geest, H. De, *see* De Geest, H.
Gehrke, J., *see* Doi, Y. *et al.*
Geizerova, H., *see* Oliver, M. F. *et al.*
Ghosh, P. K., *see* Hamilton, D. I. *et al.*
Gibson, D., *see* Chen, W. & Gibson, D.
Gibson, D. G. (& Brown, D. J.). Abnormal left ventricular wall movement in patients with chest pain and normal coronary arteriograms. *Relation to inferior T wave changes and mitral prolapse.* 385
— (& Traill, T. A., Hall, R. J. C., Brown, D. J.). Echocardiographic features of secondary left ventricular hypertrophy. 54
— *see also* Traill, T. A. *et al.*
  Vinson, C. A. *et al.*
Ginks, W. (& Leatham, A., Siddons, H.). Prognosis of patients paced for chronic atrioventricular block. 633
— (& Redwood, D. R.). Haemodynamic effects of hydralazine at rest and during exercise in patients with impaired left ventricular function. 381, *P.*
Godman, M. J., *see* Irving, J. B. & Godman, M. J.
Gold, H. K., *see* Johnson, R. A. *et al.*
Goodwin, J. F., *see* Cambridge, G. *et al.*
  Doi, Y. *et al.*
  McKenna, W. J. *et al.*
  Sanderson, J. E. *et al.*
Gopal, R., *see* Vecht, R. J. *et al.*
Gordon, S., *see* Henry, J. G. *et al.*
Gotsman, M. S., *see* Corne, R. A. *et al.*
Gottdiener, J. S., *see* Maron, B. J. *et al.*
Gourgon, R., *see* Merillon, J. P. *et al.*
Graham, I., *see* Mulcahy, R. *et al.*
Green, J., *see* Taggart, P. *et al.*
Gregory, N. L., *see* Houston, A. B. *et al.*
Greig, W. R., *see* Murray, R. G. *et al.*
Gyarfas, I., *see* Oliver, M. F. *et al.*

Hagemann, K. (& Meyer, J., Essen, R. v., Krebs, W., Effert, S.). Left ventricular ejection power in coronary artery disease during atrial pacing. 231
Hall, R. J. C. (& Clarke, S. E., Brown, D.). Evaluation of posterior aortic wall echogram in diagnosis of mitral valve disease. 522
— *see also* Gibson, D. G. *et al.*
Hallidie-Smith, K. A., *see* Ahmad, M. & Hallidie-Smith, K. A.
  MacArthur, C. G. C. *et al.*
Hamanaka, Y., *see* Matsuo, M. *et al.*
Hamilton, C. A., *see* Watson, R. D. S. *et al.*
Hamilton, D. I. (& Ghosh, P. K., Donnelly, R. J.). An operation for anomalous origin of left coronary artery: case report. 121
— *see also* Di Eusanio, G. *et al.*
Hammer, W. J., *see* Maron, B. J. *et al.*
Harper, R. W., *see* Johnson, R. A. *et al.*
Hastreiter, A. R., *see* Thanopoulos, B. D. *et al.*
Haworth, S. G. (& Radley-Smith, R., Yacoub, M.). Lung biopsy in congenital heart disease: improved clinicopathological correlations. 362, *P.*
Hayward, R. P., *see* Stephens, J. D. *et al.*
Heady, J. A., *see* Oliver, M. F. *et al.*
Hellstrom, H. R. Coronary artery vasospasm: the likely immediate cause of acute myocardial infarction. 426
Henriksson, P. (& Värendh, G., Lundström, N-R.). Haemostatic defects in cyanotic congenital heart disease. 23
Henry, J. G. (& Gordon, S., Timmis, G. C.). Corrected transposition of great vessels and Ebstein's anomaly of tricuspid valve. *Echocardiographic findings:* case report. 249
Hermens, W. T., *see* Van Der Laarse, A. *et al.*
Herwaarden, C. L. A. Van, *see* Van Herwaarden, C. L. A.
Hess, O. M., *see* Krayenbuehl, H. P. *et al.*
Hickey, N., *see* Mulcahy, R. *et al.*
Hilson, A. J. W., *see* Wainwright, R. J. *et al.*
Ho, S. Y. (& Anderson, R. H.). Coarctation, tubular hypoplasia, and the ductus arteriosus. *Histological study of 35 specimens.* 268, 361, *P.*
— (& Munro, J. L., Anderson, R. H.). Disposition of the sinus node in left-sided juxtaposition of the atrial appendages. 129
— *see also* Anderson, K. R. *et al.*
Hobbins, S. M. (& Izukawa, T., Radford, D. J., Williams, W. G., Trusler, G. A.). Conduction disturbances after surgical correction of ventricular septal defect by the atrial approach. 289
Holen, J. (& Simonsen, S.). Determination of pressure gradient in mitral stenosis with Doppler echocardiography. 529
Hollaar, L., *see* Van Der Laarse, A. *et al.*
Holmgren, A., *see* Åström, H. *et al.*
Honey, M., *see* Brooks, N. *et al.*
Hori, M. (& Inoue, M., Fukui, S., Shimazu, T., Mishima, M., Ohgitani, N., Minamino, T., Abe, H.). Correlation of ejection fraction and infarct size estimated from the total CK released in patients with acute myocardial infarction. 433

Houlsby, W. T., *see* Dickinson, D. F. *et al.*
Houston, A. B. (& Gregory, N. L., Coleman, E. N.). Echocardiographic identification of aorta and main pulmonary artery in complete transposition: correspondence. 356, 631
Hugenholtz, P. G., *see* Ten Cate, F. J. *et al.*
Hume, L. (& Ewing, D. J., Campbell, I. W., Reuben, S. R., Clarke, B. F.). Non-invasive assessment of left ventricular response to Valsalva manoeuvre in normal and diabetic subjects using praecordial accelerocardiography. 199
Hunt, D. Effects of atrial fibrillation on prognosis of acute myocardial infarction: correspondence. 225
Hutter, jun., A. M., *see* Johnson, R. A. *et al.*
Hutton, I., *see* Murray, R. G. *et al.*

Imeson, J. D., *see* Meade, T. W. *et al.*
Inbar-Yanai, I., *see* Cristal, N. *et al.*
Inoue, M., *see* Hori, M. *et al.*
Matsuo, M. *et al.*
Ionescu, M. I., *see* Thomas, R. D. *et al.*
Irving, J. B. (& Godman, M. J.). Exercise testing and ambulatory electrocardiographic monitoring after surgical repair of Fallot's tetralogy and ventricular septal defect. 368, *P.*
Ivey, H. H. (& Kattwinkel, J., Park, T. S., Krovetz, L. J.). Failure of indomethacin to close persistent ductus arteriosus in infants weighing under 1000 grams. 304
Izukawa, T., *see* Hobbins, S. M. *et al.*

Jackson, G., *see* Bergman, G. W. *et al.*
Rothman, M. *et al.*
Jaffe, A. S., *see* Ahumada, G. G. *et al.*
Jarritt, P. H., *see* Dymond, D. S. *et al.*
Jenkins, B. S., *see* Shiu, M. F. *et al.*
Jenkins, J. S., *see* Mather, H. M. *et al.*
Jennings, K. P., *see* McLeod, A. A. *et al.*
Jewitt, D. E., *see* Bergman, G. W. *et al.*
Rothman, M. *et al.*
Jimenez, M. Q., *see* Tynan, M. J. *et al.*
Johnson, R. A. (& Zir, L. M., Harper, R. W., Leinbach, R. C., Hutter, jun., A. M., Pohost, G. M., Block, P. C., Gold, H. K.). Patterns of haemodynamic alteration during left ventricular ischaemia in man. *Relation to angiographic extent of coronary artery disease.* 441
— *see also* Boucher, C. A. *et al.*
Johnston, P. G. B., *see* Southall, D. P. *et al.*
Jones, D. H., *see* Watson, R. D. S. *et al.*
Jonsson, B., *see* Åström, H. *et al.*
Joransen, J. A. (& Lucas, Jr., R. V., Moller, J. H.). Postoperative haemodynamics in tetralogy of Fallot. *A study of 132 children.* 33
Jordan, R. M. (& McAnulty, J. H., Ritzmann, L.). Alternating atrial and ventricular tachycardia: case report. 734
Joseph, S., *see* Ross, P. *et al.*
Joseph, S. P., *see* Taggart, P. *et al.*
Julian, D. G., *see* Vetter, N. J. *et al.*

Kappenberger, L. (& Sowton, E.). Method for control of tachycardia by long-term programmed stimulation. 371, *P.*
Karliner, J. S., *see* Ryan, W. F. & Karliner, J. S.
Karlsberg, R. P., *see* Ahumada, G. G. *et al.*
Kasturi, T. E. (& Manchanda, S. C., Tandon, R. K., Rajani, M., Bhatia, M. L.). Haemodynamic studies in veno-occlusive disease of the liver. 594
Kattwinkel, J., *see* Ivey, H. H. *et al.*
Keeton, B. R., *see* Shinebourne, E. A. *et al.*
Kelly, H. B., *see* Taggart, P. *et al.*
Kesteloot, H., *see* Willems, J. L. H. *et al.*
Khan, M., *see* Vasquez, M. *et al.*
Kilpatrick, D., *see* Talbot, S. *et al.*
Kinney, E. (& Reeves, W., Berman, W., jun., Zelis, R.). Echocardiographic visualisation of the interatrial baffle after Mustard's operation: correspondence. 359
Kitchin, A. H., *see* Sang, C. T. M. *et al.*
Koch, G. Haemodynamic adaptation at rest and during exercise to long-term antihypertensive treatment with combined alpha- and beta-adrenoreceptor blockade by labetalol. 192
Komatsu, Y., *see* Satomi, G. *et al.*
Krayenbuehl, H. P. (& Turina, M., Hess, O. M., Rothlin, M., Senning, Å.). Pre- and postoperative left ventricular contractile function in patients with aortic valve disease. 204
Krebs, W., *see* Hagemann, K. *et al.*
Krediet, R. T. (& Dunning, A. J.). Baroreflex sensitivity in hypertension during beta-adrenergic blockade. 106
Krikler, D. M., *see* Bentall, H. H. *et al.*
Rowland, E. *et al.*
Krovetz, L. J., *see* Ivey, H. H. *et al.*
Kulbertus, H. E., *see* Waleffe, A. *et al.*

Laar, A. van't, *see* Van Herwaarden, C. L. A. *et al.*
Laarse, van der, A., *see* Van Der Laarse, A.
Lachman, A. S., *see* McLaren, M. J. *et al.*
Lam, L., *see* Shinebourne, E. A. *et al.*
Langevin, E., *see* Chandraratna, P. A. N. *et al.*
Laragh, J. H., *see* Davies, R. *et al.*
Lavecchia, G., *see* Brevetti, G. *et al.*
Lavender, J. P., *see* MacArthur, C. G. C. *et al.*
Layton, C. A. (& Stockley, A. V.). Computer processed thallium-201 scintigrams during and 4 hours after maximal exercise. Significance of stenosed and occluded vessels. 368, *P.*
Lawrie, T. D. V., *see* Murray, R. G. *et al.*
Leatham, A., *see also* Brooks, N. *et al.*
Ginks, W. *et al.*
Mills, P. *et al.*
Leech, G., *see* Brooks, N. *et al.*
Mills, P. *et al.*
— *see* Mills, P. *et al.*
Leenage, R., *see* Shinebourne, E. A. *et al.*
Leinbach, R. C., *see* Johnson, R. A. *et al.*
Leval, M. de, *see* De Leval, M.
Lie, K. I., *see* Wackers, F. J. Th. *et al.*
Liem, K. L., *see* Wackers, F. J. Th. *et al.*
Lincoln, C., *see* Crupi, G. *et al.*
— *see* Shinebourne, E. A. *et al.*
Littler, W. A., *see* Evemy, K. L. *et al.*
Watson, R. D. S. *et al.*
Llera, J. J., *see* Suarez, L. D. *et al.*
Loewy, E. H. Effects of atrial fibrillation on prognosis of acute myocardial infarction: correspondence. 255
Lopez, R. *see* Maddison, A. *et al.*
Yusuf, S. *et al.*
Lorimer, A. R., *see* Murray, R. G. *et al.*
Lucas, R. V., *see* Joransen, J. A. *et al.*
Lukes, S. A. (& Romero, C. A., Resnekov, L.). Haemodynamic effects of sodium nitroprusside in 21 subjects with congestive heart failure. 187
Lundström, N-R., *see* Henriksson, P. *et al.*

McAnulty, J. H., *see* Jordan, R. M. *et al.*
MacArthur, C. G. C. (& Pratt, T. A., Lavender, J. P., Hallidie-Smith, K. A., Oakley, C. M.). Lung scan abnormalities in hypertensive pulmonary vascular disease. 362, *P.*
— *see also* Cambridge, G. *et al.*
Macartney, F. J., *see* McNicholas, K. *et al.*
— *see also* Tynan, M. J. *et al.*

Macartney, F., *see* Morrison, G. & Macartney, F.
McHenry, M. M. (& Rice, J., Matlof, H. J., Flamm, Jun., M. D.). Pulmonary hypertension and sudden death in aortic stenosis. 463
McKenna, W., *see* Doi, Y. *et al.*
McKenna, W. J. (& Chetty, S., Oakley, C. M., Goodwin, J. F.). Exercise electrocardiographic and 48-hour ambulatory electrocardiographic monitor assessment of arrhythmia on and off beta-blocker therapy in hypertrophic cardiomyopathy. 375, *P.*
McKillop, J. H., *see* Murray, R. G. *et al.*
Mackintosh, A. F. Sinus node disease in young people. 372, *P.*
McLaren, M. J. (& Lachman, A. S., Barlow, J. B.). Prevalence of congenital heart disease in black schoolchildren of Soweto, Johannesburg. 554
McLeod, A. A. (& Jennings, K. P., Townsend, E. R.). Near fatal puerperal thrombosis on Björk-Shiley mitral valve prosthesis: correspondence. 630
McNicholas, A. (& de Leval, M., Stark, J., Taylor, J. F. N., Macartney, F. J.). Surgical treatment of ventricular septal defect in infancy. *Primary repair versus banding of pulmonary artery and later repair.* 133
Maddison, A. (& Yusuf, S., Lopez, R., Sleight, P., Craig, A.). Serum myoglobin determination in patients with acute myocardial infarction. 370, *P.*
Maisey, M. N., *see* Pitcher, D. W. *et al.*
Wainwright, R. J. *et al.*
Manchanda, S. C., *see* Kasturi, T. E. *et al.*
Mann, S. (& Craig, M. M., Balasubramanian, V., Raftery, E. B.). Nocturnal blood pressure in hypertensives and effects of alpha- and beta-adrenergic blockade. 384, *P.*
Marcomichelakis, J., *see* Taggart, P. *et al.*
Maron, B. J. (& Gottdiener, J. S., Roberts, W. C., Hammer, W. J., Epstein, S. E.). Nongenetically transmitted disproportionate ventricular septal thickening associated with left ventricular outflow obstruction. 345
Marquez, J., *see* Coto, E. O. *et al.*
Martin, M. A. (& Fieller, N. R. J.) Echocardiography in cardiovascular drug assessment. 536
Mary, D. A. S., *see* Thomas, R. D. *et al.*
Maseri, A., *see* Parodi, O. *et al.*
Mather, H. M. (& Boyd, M. J., Jenkins, J. S.). Heart size and function in acromegaly. 697
Matlof, H. J., *see* McHenry, M. M. *et al.*
Matsumoto, M., *see* Matsuo, M. *et al.*
Matsuo, H. (& Matsumoto, M., Hamanaka, Y., Ohara, T., Senda, S., Inoue, M., Abe, H.). Rotational excursion of heart in massive pericardial effusion studied by phased-array echocardiography. 513
Meade, T. W. (& Chakrabarti, R., Imeson, J. D., Stirling, Y., Vickers, M., Stewart, G. M.). Fibrinolytic activity on Monday and on other days of the week. 375, *P.*
Mehra, R. (& Furman, S.). Comparison of cathodal, anodal, and bipolar strength-interval curves with temporary and permanent pacing electrodes. 468
Merillon, J. P. (& Motte, G., Aumont, M. C., Prasquier, R., Gourgon, R.). Study of left ventricular pressure-volume relations during nitroprusside infusion in human subjects without coronary artery disease. 325
Meyer, J., *see* Hagemann, K. *et al.*
Miller, H. C., *see* Cotter, L. & Miller, H. C.
Sang, C. T. M. *et al.*
Mills, P. (& Davis, A., Leech, G., Davies, M., Parker, J., Leatham, A.). Correlation of echocardiographic, surgical, and pathological findings in mitral regurgitation. 374, *P.*
— (& Woolfe, C., Redwood, D., Leech, G., Craige, E., Leatham, A.). Non-invasive diagnosis of infundibular right ventricular outflow tract obstruction. 382, *P.*
Minamino, T., *see* Hori, M. *et al.*
Mishima, M., *see* Hori, M. *et al.*
Mitko, A., *see* Shackell, M. *et al.*
Mittra, S., *see* Taylor, K. M. *et al.*
Moller, J. H., *see* Joransen, J. A. *et al.*
Monro, J. L., *see* Ho, S. Y. *et al.*
Morgan, A., *see* Davies, G. J. *et al.*
Morganti, A., *see* Davies, R. *et al.*
Morris, J. N., *see* Oliver, M. F. *et al.*
Morrison, G. (& Macartney, F.). Effects of oxygen administration, bicarbonate infusions, and brief hyperventilation on patients with pulmonary vascular obstructive disease. 584
Morton, J. J., *see* Taylor, K. M. *et al.*
Motte, G., *see* Merillon, J. P. *et al.*
Muir, J. R., *see* Davies, G. J. *et al.*
Mulcahy, R. (& Graham, I., Hickey, N.). Influence of cigarette smoking on morbidity, mortality, and mode of death in coronary patients. 365, *P.*
Murray, R. G. Quantitative approach to analysis of exercise thallium-201 scintigraphy: clinical evaluation. 360, *P.*
— (& McKillop, J. H., Bessent, R. G., Turner, J. G., Lorimer, A. R., Hutton, I., Greig, W. R., Lawrie, T. D. V.). Evaluation of thallium-201 exercise scintigraphy in coronary heart disease. 568
— — Tweddel, A., Turner, J. G., Bessent, R. G., Hutton, I., Lorimer, A. R.). Value of thallium-201 exercise scintigraphy in predicting coronary artery graft status. 369, *P.*

Narula, O. S., *see* Vasquez, M. *et al.*
Nayler, W. G., *see* Petch, M. C. & Nayler, W. G.
Nazarian, J., *see* Daneshwar, A. *et al.*
Noakes, T. D. (& Rose, A. G., Opie, L. H.). Hypertrophic cardiomyopathy associated with sudden death during marathon racing: case report. 624
Noble, D., *see* Taggart, P. *et al.*
Nordlander, R. (& Nyquist, O.). Patients treated in a coronary care unit without acute myocardial infarction. 647
Nyberg, G. (& Vedin, A., Wilhelmsson, C.). QT time in patients treated with alprenolol or placebo after myocardial infarction. 452
Nyquist, O., *see* Nordlander, R. & Nyquist, O.

Oakley, C. M., *see* Cambridge, G. *et al.*
MacArthur, C. G. C. *et al.*
McKenna, W. J. *et al.*
Oakley, D. (& Selwyn, A. P., Forse, G., Steiner, R.). Pattern of disturbed regional myocardial perfusion in patients with coronary artery disease. 376, *P.*
— *see also* Selwyn, A. P. *et al.*
Oberhänsli, I. (& Friedli, B.). Echocardiographic study of right and left ventricular dimension and left ventricular function in patients with tetralogy of Fallot before and after surgery. 40
Ogawa, T., *see* Figueras, J. *et al.*
Ohara, T., *see* Matsuo, M. *et al.*
Ohgitani, N., *see* Hori, M. *et al.*
O'Neill, G., *see* Taggart, P. *et al.*
Oliver, M. F. (& Geizerova, H., Gyarfas, I., Heady, J. A., Morris, J. N., Strasser, T.). Co-operative trial in primary prevention of ischaemic heart disease using clofibrate. 363, *P.*
Opie, L. H., *see* Noakes, T. D. *et al.*
O'Riordan, J. (& Stark, J., de Leval, M.). Indications and results of Fontan operation and its modifications. 366, *P.*
O'Rourke, M. F. (& Sammel, N., Chang, V. P.). Arterial counterpulsation in severe refractory heart failure complicating acute myocardial infarction. 308

Osnaya, H. (& Somerville, J.). Tricuspid atresia. Early and late problems after pulmonary artery to right atrial connection. 365, *P.*

Pantridge, J. F., *see* Campbell, N. P. S. *et al.*
Park, T. S., *see* Ivey, H. H. *et al.*
Parker, J., *see* Mills, P. *et al.*
Parodi, O. (& Maseri, A., Simonetti, I.). Management of unstable angina at rest by verapamil. *A double-blind cross-over study in coronary care unit.* 167
Parry, E. H. O., *see* Sanderson, J. E. *et al.*
Patterson, G. C., *see* Campbell, N. P. S. *et al.*
Patton, J. N. Ventricular defibrillation. 361, *P.*
Peploe, M. M. Webb, *see* Webb-Peploe, M. M.
Perosio, A. M., *see* Suarez, L. D. *et al.*
Petch, M. C. (& Nayler, W. G.). Concentration of catecholamines in human cardiac muscle. 340
— — Uptake of catecholamines by human cardiac muscle in vitro. 336
Peterburg, I., *see* Cristal, N. *et al.*
Philip, G., *see* Vecht, R. J. *et al.*
Pickering, D., *see* Cooke, R. W. I. & Pickering, D.
Pickering, T. G., *see* Davies, R. *et al.*
Pitcher, D. W. (& Wainwright, R. J., Maisey, M. N., Currey, P. V. L., Sowton, E.). Assessment of chest pain in hypertrophic cardiomyopathy by thallium-201 myocardial scintigraphy. 379, *P.*
Pocock, S., *see* Vetter, N. J. *et al.*
Pohost, G. M., *see* Johnson, R. A. *et al.*
Poole-Wilson, P. A. (& Bourdillon, P. D. V., Foale, R. A., Timmis, A. D., Sutton, G. C.). Salbutamol in treatment of heart failure. 380, *P.*
— *see also* Baron, D. W. *et al.*
Prasquier, R., *see* Merillon, J. P. *et al.*
Pratt, T. A., *see* MacArthur, C. G. C. *et al.*

Radford, D. J., *see* Hobbins, S. M. *et al.*
Radley-Smith, R., *see* Haworth, S. G. *et al.*
Raftery, E. B., *see* Mann, S. *et al.*
Rajah, S. M. (& Rao, S., Ahmad, R., Watson, D. A.). Near fatal puerperal thrombosis on Björk-Shiley mitral valve prosthesis: correspondence, 630
Rajani, M., *see* Kasturi, T. E. *et al.*
Rao, S., *see* Rajah, S. M. *et al.*
Raper, D. A., *see* Wainwright, R. J. *et al.*
Ray, S. C., *see* Di Eusanio, G. *et al.*
Redwood, D. R., *see* Ginks, W. R. & Redwood, D. R.
Mills, P. *et al.*
Reeves, W., *see* Kinney, E. *et al.*
Reid, J. L., *see* Watson, R. D. S. *et al.*
Reid, J. M. (& Murdoch, R.). Polymyositis and complete heart block: case report. 628
Rengo, F., *see* Brevetti, G. *et al.*
Resnekov, L., *see* Lukes, S. A. *et al.*
Reuben, S. R., *see* Hume, L. *et al.*
Rice, J., *see* McHenry, M. M. *et al.*
Richards, J. M., *see* Southall, D. P. *et al.*
Rickards, A. F. (& Baron, D. W., Canepa-Anson, R.). Glyceryl trinitrate vs post-ectopic potentiation in assessment of ischaemic left ventricle. 377, *P.*
— *see also* Baron, D. W. *et al.*
Bourdillon, P. D. V. *et al.*
Davies, A. B. *et al.*
Foale, R. A. *et al.*
Rigby, M. L., *see* Silove, E. D. *et al.*
Ritzmann, L., *see* Jordan, R. M. *et al.*
Roberts, K. D., *see* Silove, E. D. *et al.*
Roberts, R., *see* Ahumada, G. G. *et al.*
Roberts, W. C. Quantification of coronary heart disease. 363, *P.*
— *see also* Maron, B. J. *et al.*
Roelandt, J., *see* Ten Cate, F. J. *et al.*
Romero, C. A., *see* Lukes, S. A. *et al.*
Rose, A. G., *see* Noakes, T. D. *et al.*
Ross, D. N., *see* Bennett, G. *et al.*
Ross, P. (& Joseph, S., Walker, D.). A case of isolated primary chylopericardium: case report. 508
Rothlin, M., *see* Krayenbuehl, H. P. *et al.*
Rothman, M. (& Bergman, G., Atkinson, L., Jackson, G., Jewitt, D. E.). Value and limitation of ergometrine in predicting vasospastic angina. 370, *P.*
Rowland, E. (& Dawson, R., Krikler, D. M.). Amiodarone in prophylaxis of various supraventricular arrhythmias. 372, *P.*
— *see also* Bentall, H. H. *et al.*
Talbot, S. *et al.*
Rowlands, D. J., *see* Brunt, J. N. H. *et al.*
Walton, S. *et al.*
Rufilanchas, J. J., *see* Coto, E. O. *et al.*
Ryan, W. F. (& Karliner, J. S.). Effects of tocainide on left ventricular performance at rest and during acute alterations in heart rate and systemic arterial pressure. An echocardiographic study. 175

Salomon, J. A., *see* Corne, R. A. *et al.*
Sammel, N., *see* O'Rourke, M. F. *et al.*
Samson, G., *see* Wackers, F. J. Th. *et al.*
Samuels, L. D., *see* Corne, R. A. *et al.*
Sanderson, J. E. (& Adesanya, C. O., Anjorin, F. I., Parry, E. H. O., Goodwin, J. F.). Left ventricular function in postpartum cardiac failure syndrome of northern Nigeria. 378, *P.*
Sang, C. T. M. (& Wallwork, J., Miller, H. C., Kitchin, A. H., Davison, K. G., Caves, P. K.). Early clinical experience with the Hancock porcine xenograft valve prosthesis. 226
Satomi, G. (& Shimizu, K., Komatsu, Y., Takao, A.). Echocardiographic identification of aorta and main pulmonary artery in complete transposition: correspondence. 356
Schlepper, M., *see* Sesto, M. *et al.*
Schoot, J. van der, *see* van der Schoot, J.
Schwarz, F., *see* Sesto, M. *et al.*
Sciandro, E. E., *see* Suarez, L. D. *et al.*
Selwyn, A., *see* Fox, K. M. *et al.*
Selwyn, A. P. (& Fox, K. M., Oakley, D., Shillingford, J. P.). Assessment of myocardial ischaemia in ambulatory patients with daily chest pain. 376, *P.*
— *see also* Oakley, D. *et al.*
Senda, S., *see* Matsuo, M. *et al.*
Senning, Å., *see* Krayenbuehl, H. P. *et al.*
Sesto, M. (& Schwarz, F., Thiedemann, K-U., Flameng, W., Schlepper, M.). Failure of aneurysmectomy to improve left ventricular function. 79
Shackell, M. (& Mitko, A., Williams, P. L., Sutton, G. C.). Angiosarcoma of the heart. 498
Shantha, N., *see* Vasquez, M. *et al.*
Sharkey, J., *see* Falk, R. H. *et al.*
Shields, R. A., *see* Walton, S. *et al.*
Shillingford, J. P., *see* Fox, K. M. *et al.*
Selwyn, A. P. *et al.*
Shimazu, T., *see* Hori, M. *et al.*
Shimizu, K., *see* Satomi, G. *et al.*
Shinebourne, E. A. (& Southall, D. P., Keeton, B. R., Leanage, R., Lam, L., Lincoln, C.). Arrhythmias and Mustard's operation. 367, *P.*
— *see also* de Swiet, M. *et al.*
Southall, D. P. *et al.*
Tynan, M. J. *et al.*

SHIU, M. F. (& Coltart, D. J., Braimbridge, M. V.). Echocardiographic findings in prolapsed aortic cusp with vegetation: case report. 118

— (& Crowther, A., Jenkins, B. S., Webb-Peploe, M. M.). Echocardiographic and exercise evaluation of results of mitral valvotomy operations. 139

SIDDONS, H., *see* Ginks, W. *et al.*

SILOVE, E. D. (& Rigby, M. L., Clarke, D. B., Abrams, L. D., Roberts, K. D., Singh, S. P., Astley, R.). Critical aortic stenosis in early infancy. 367, *P.*

SIMONETTI, I., *see* Parodi, O. *et al.*

SIMONSEN, S., *see* Holen, J. & Simonsen, S.

SINGH, B. N., *see* Figueras, J. *et al.*

SINGH, S. P. (& Astley, R.). Severe complication of pulmonary vein angiography: correspondence, 740

— *see also* Silove, E. D. *et al.*

SLEIGHT, P., *see* Maddison, A. *et al.*
    Yusuf, S. *et al.*

SMITH, K. A. HALLIDIE-, *see* Hallidie-Smith, K. A.

SMITH, R. RADLEY-, *see* Radley-Smith, R.

SOBEL, B. E., *see* Ahumada, G. G. *et al.*

SOKOLE, E. B., *see* Wackers, F. J. Th. *et al.*

SOMERVILLE, J. Congenital heart disease—changes in form and function. 1

— Fixed (discrete) subaortic stenosis—late results of resection. A congenital or acquired lesion? 366, *P.*

— *see also* Foale, R. A. *et al.*
    Osnaya, H. & Somerville, J.
    Taggart, P. *et al.*

SOMERVILLE, W., *see* Thompson, R. *et al.*

SOUTHALL, D. P. (& Richards, J. M., Johnston, P. G. B., Shinebourne, E. A.). Study of cardiac rhythm in healthy newborn infant. 382, *P.*

— *see also* Shinebourne, E. A. *et al.*

SOWTON, E., *see* Kappenberger, L. & Sowton, E.
    Pitcher, D. W. *et al.*
    Wainwright, R. J. *et al.*

SPODICK, D. H. Systolic time intervals and impedance cardiography: correspondence. 253

SPURRELL, R. A. J., *see* Camm, A. J. *et al.*
    Dymond, D. S. *et al.*
    Stephens, J. D. *et al.*
    Wang, R. *et al.*

STALLARD, T. J., *see* Watson, R. D. S. *et al.*

STARK, J., *see* McNicholas, K. *et al.*
    O'Riordan, J. *et al.*

STEINER, R., *see* Oakley, D. *et al.*

STEPHENS, J. D. (& Banim, S. O., Spurrell, R. A. J.). Haemodynamic effects of sublingual isosorbide dinitrate and oral salbutamol alone and in combination in patients with severe chronic congestive cardiac failure. 381, *P.*

— (& Hayward, R. P., Dymond, D. S., Ead, H., Adams, L., Spurrell, R. A. J.). Effects of sodium nitroprusside and phenylephrine on coronary dynamics in patients with normal left ventricular function. 456

STEWART, G. M., *see* Meade, T. W. *et al.*

STIRLING, Y., *see* Meade, T. W. *et al.*

STOCKLEY, A. V., *see* Layton, C. A. & Stockley, A. V.

STONE, D. L., *see* Dymond, D. S. *et al.*

STRASSER, T., *see* Oliver, M. F. *et al.*

STURRIDGE, M., *see* Brooks, N. *et al.*

STURRIDGE, M. F., *see* Vaughton, K. C. *et al.*

SUAREZ, L. D. (& Sciandro, E. E., Llera, J. J., Perosio, A. M.). Long-term follow-up in primary pulmonary hypertension. 702

SUTTON, G. C., *see* Poole-Wilson, P. A. *et al.*
    Shackell, M. *et al.*

SUTTON, M. G. St. J., *see* Traill, T. A. *et al.*

SUTTON, R. (& Citron, P.). Electrophysiological and haemodynamic basis for application of new pacemaker technology in sick sinus syndrome and atrioventricular block. 600

SWAN, H. J. C., *see* Figueras, J. *et al.*

SWIET, M. DE, *see* de Swiet, M.

SYMONS, C. Thyroid heart disease. Editorial. 257

TAGGART, P. (& Carruthers, M., Joseph, S., Kelly, H. B., Marcomichelakis, J., Noble, D., O'Neill, G., Somerville, W.). Electrocardiographic changes resembling myocardial ischaemia in asymptomatic men with normal coronary arteriograms. 214

— — Donaldson, R., Green, J., Joseph, S. P., Kelly, H. B., Marcomichelakis, J., Noble, D., White, J., Somerville, W.). Ischaemic-like electrocardiogram in asymptomatic men with normal coronary arteriogram: studies by atrial pacing, adrenaline infusion, and autonomic blockade. 376, *P.*

TAKAO, A., *see* Satomi, G. *et al.*

TALBOT, S. (& Kilpatrick, D., Rowland, E.). Differentiation of ventricular ectopy from aberration. 372, *P.*

TANDON, R. K., *see* Kasturi, T. E. *et al.*

TAVAKOLI, D., *see* Daneshwar, A. *et al.*

TAYLOR, C. J., *see* Brunt, J. N. H. *et al.*

TAYLOR, J. F. N., *see* McNicholas, K. *et al.*

TAYLOR, K. M. (& Casals, J., Morton, J. J., Mittra, S., Brannan, J. J., Bain, W. H.). Haemodynamic effects of angiotensin blockade after cardiopulmonary bypass. 380, *P.*

TAYLOR, W. R., *see* Figueras, J. *et al.*

TEN CATE, F. J. (& van Dorp, W. G., Hugenholtz, P. G., Roelandt, J.). Fixed subaortic stenosis. *Value of echocardiography for diagnosis and differentiation between various types.* 159

TESTA, H. J., *see* Walton, S. *et al.*

THANOPOULOS, B. D. (& Dubrow, I. W., Fisher, E. A., Hastreiter, A. R.). Double outlet right ventricle with subvalvular aortic stenosis: case report. 241

THIEDEMANN, K-U., *see* Sesto, M. *et al.*

THOMAS, R. D. (& Mary, D. A. S., Ionescu, M. I.). Echocardiographic pattern of posterior mitral valve leaflet movement after mitral valve repair. 399

THOMPSON, R. (& Ahmed, M., Somerville, W., Towers, M., Yacoub, M.). Use of fresh unstented homograft valves for replacement of aortic valve. Analysis of 8 years' experience. 374, *P.*

TIMMIS, A. D., *see* Poole-Wilson, P. A. *et al.*

TIMMIS, G. C., *see* Henry, J. G. *et al.*

TOWERS, M., *see* Thompson, R. *et al.*

TOWNSEND, E. R., *see* McLeod, A. A. *et al.*

TRAILL, T. A. (& Sutton, M. G. St. J., Gibson, D. G.). Mitral stenosis with high left ventricular diastolic pressure. 405

— *see also* Gibson, D. G. *et al.*

TRUSLER, G. A., *see* Hobbins, S. M. *et al.*

TURINA, M., *see* Krayenbuehl, H. P. *et al.*

TURNER, J. G., *see* Murray, R. G. *et al.*

TWEDDEL, A., *see* Murray, R. G. *et al.*

TYNAN, M. J. (& Becker, A. E., Macartney, F. J., Jiménez, M. Q., Shinebourne, E. A., Anderson, R. H.). Nomenclature and classification of congenital heart disease. 544

VALK, VAN DER, E. J. M., *see* Van Der Valk, E. J. M.

VAN DER LAARSE, A. (& Davids, H. A., Hollaar, L., Van Der Valk, E. J. M., Witteveen, S. A. G. J., Hermens, W. T.). Recognition and quantification of myocardial injury by means of plasma enzyme and isoenzyme activities after cardiac surgery. 660

VAN DER SCHOOT, J., *see* Wackers, F. J. Th. *et al.*

VAN DER VALK, E. J. M., *see* Van Der Laarse, A. *et al.*
VAN DORP, W. G., *see* Ten Cate, F. J. *et al.*
VAN HERWAARDEN, C. L. A. (& Binkhorst, R. A., Fennis, J. F. M., Laar, A. van't). Effects of propranolol and metoprolol on haemodynamic and respiratory indices and on perceived exertion during exercise in hypertensive patients. 99
VAN'T LAAR, A., *see* Laar, A. van't
VÄRENDH, G., *see* Henriksson, P. *et al.*
VARNAUSKAS, E. Multicentre prospective randomised study of coronary bypass surgery in angina pectoris. Survival at 2 years. 363, *P.*
VASQUEZ, M. (& Chuquimia, R., Shantha, N., Khan, M., Narula, O. S.). Clinical electrophysiological effects of propranolol on normal sinus node function. 709
VAUGHTON, K. C. (& Walker, D. R., Sturridge, M. F.). Mitral valve replacement for mitral stenosis caused by Libman-Sacks endocarditis: case report. 730
VECHT, R. J. (& Carmichael, D. J. S., Gopal, R., Philip, G.). Uhl's anomaly. 676
VEDIN, A., *see* Nyberg, G. *et al.*
VETTER, N. J. (& Pocock, S., Julian, D. G.). Measuring the effect of a mobile coronary care unit upon the community. 418
VICKERS, M., *see* Meade, T. W. *et al.*
VINSON, C. A. (& Gibson, D. G., Yettram, A. L.). Analysis of left ventricular behaviour in diastole by means of finite element method. 60
VLAHOVICH, G., *see* Chandraratna, P. A. N. *et al.*

WACKERS, F. J. TH. (& Lie, K. I., Liem, K. L., Sokole, E. B., Samson, G., van der Schoot, J., Durrer, D.). Potential value of thallium-201 scintigraphy as means of selecting patients for the coronary care unit. 111
WAINWRIGHT, R. Functional significance of coronary collateral circulation during dynamic exercise evaluated by thallium-201 myocardial scintigraphy. 360, *P.*
WAINWRIGHT, R. J. (& Raper, D. A., Cueni, T. A., Hilson, A. J. W., Maisey, M. N., Sowton, E.). Ventricular function in response to cold pressor test: assessment using multiple gated acquisition on technetium-99m labelled cardiac blood pool (MUGA-99Tcm) in normal subjects and patients with ischaemic heart disease. 378, *P.*
— *see also* Pitcher, D. W. *et al.*
WALEFFE, A. (& Bordalo, A., Bruninx, P., Wellens, H. J. J., Kulbertus, H. E.). Electrophysiological effects of L 9394 (benzoyl-indolizine) in man. 89
WALKER, D., *see* Ross, P. *et al.*
WALKER, D. R., *see* Vaughton, K. C. *et al.*
WALLWORK, J., *see* Sang, C. T. M. *et al.*
WALMSLEY, R. Anatomy of left ventricular outflow tract. 263
WALTON, S. (& Rowlands, D. J., Shields, R. A., Testa, H. J., Wrigley, C.). Limitations of gated blood pool scintigraphy: clinical and experimental aspects. 373, *P.*
WANG, R. (& Ward, D. E., Camm, A. J., Spurrell, R. A. J.). Value of 24-hour ambulatory electrocardiographic recordings in 405 patients with dizziness, syncope, or palpitation. 373, *P.*
WARD, D. E., *see* Wang, R. *et al.*
WARSHAW, B., *see* Corne, R. A. *et al.*
WATERSON, A. P., *see* Cambridge, G. *et al.*
WATSON, D. A., *see* Rajah, S. M. *et al.*
WATSON, R. D. S. (& Hamilton, C. A., Jones, D. H., Stallard, T. J., Reid, J. L., Littler, W. A.). Cardiovascular and sympathetic adaptation with bicycle exercise. 383, *P.*
WEBB-PEPLOE, M. M., *see* Shiu, M. F. *et al.*
WEISS, A., *see* Corne, R. A. *et al.*
WELLENS, H. J. J., *see* Waleffe, A. *et al.*
WHITE, J., *see* Taggart, P. *et al.*
WILHELMSSON, C., *see* Nyberg, G. *et al.*
WILKINSON, J. L., *see* Coto, E. O. *et al.*
Dickinson, D. F. *et al.*
WILLEMS, J. L. H. (& Denef, B., Kesteloot, H., De Geest, H.). Comparability and reproducibility of apex cardiogram recorded with six different transducer systems. 716
WILLIAMS, P. L., *see* Shackell, M. *et al.*
WILLIAMS, W. G., *see* Hobbins, S. M. *et al.*
WILSON, M., *see* Davies, R. *et al.*
WILSON, P. A. POOLE-, *see* Poole-Wilson, P. A.
WITTEVEEN, S. A. G. J., *see* Van Der Laarse, A. *et al.*
WOOLFE, C., *see* Mills, P. *et al.*
WRIGHT, J., *see* Brooks, N. *et al.*
WRIGLEY, C., *see* Walton, S. *et al.*

YACOUB, M., *see* Haworth, S. G. *et al.*
Thompson, R. *et al.*
YACOUB, M. H., *see* Bennett, G. *et al.*
YANAI, I. INBAR-, *see* Inbar-Yanai, I.
YETTRAM, A. L., *see* Vinson, C. A. *et al.*
YURCHAK, P. M., *see* Boucher, C. A. *et al.*
YUSUF, S. (& Lopez, R., Sleight, P.). Normalisation of electrocardiogram in survivors of myocardial infarction on beta-blockers. 364, *P.*
— *see also* Maddison, A. *et al.*

ZAIDI, S. A., *see* Campbell, N. P. S. *et al.*
ZELIS, R., *see* Kinney, E. *et al.*
ZIR, L. M., *see* Johnson, R. A. *et al.*
ZUBEREUHLER, J. R. (& Anderson, R. H.). Morphological variations in pulmonary atresia with intact ventricular septum. 281

SUBJECT INDEX

1979, Volume 41

Accelerocardiogram in Valsalva manoeuvre, in normal and diabetic subjects (Hume *et al.*). 199
Acebutolol, in reduction of early ventricular arrhythmia in myocardial infarction (Ahumada *et al.*). 654
Acromegaly, heart size and function (Mather *et al.*). 697
Adrenaline infusion, atrial pacing and autonomic blockade study: ischaemic-like ECG in asymptomatic men (Taggart *et al.*). 376, *P.*
Alcoholic cardiomyopathy, glyceryl trinitrate paste inducing pulsus alternans in: case report (Chandraratna *et al.*). 354
Alpha and beta-adrenergic blockade, effects on nocturnal blood pressure in hypertensives (Mann *et al.*). 384, *P.*
Alprenolol in myocardial infarction, QT time after (Nyberg *et al.*). 452
Amiodarone in prophylaxis of various supraventricular arrhythmias (Rowland *et al.*). 372, *P.*
Aneurysms, postinfarction left ventricular, detection by radionuclide ventriculography (Dymond *et al.*). 68
Aneurysmectomy, failure to improve left ventricular function (Sesto *et al.*). 79
Angina pectoris
  assessment of myocardial ischaemia in ambulatory patients with (Selwyn *et al.*). 376, *P.*
  blood volume in (Åström *et al.*). 477
  coronary bypass surgery, multicentre prospective randomised study, survival at 2 years (Varnauskas). 363, *P.*
  recurrent, reoperation (Brooks *et al.*). 369, *P.*: risks and results (Bennett *et al.*). 370, *P.*
  unstable, at rest, verapamil in management (Parodi *et al.*). 167
  vasospastic, value and limitation of ergometrine in predicting (Rothman *et al.*). 370, *P.*
Angiography, pulmonary vein, severe complication: case report (Alpert & Culham). 727: correspondence (Singh & Astley). 740
Angiosarcoma of the heart (Shackell *et al.*). 498
Angiotensin blockade after cardiopulmonary bypass, haemodynamic effects (Taylor *et al.*). 380, *P.*
Aorta (aortic)
  coarctation, *see* Coarctation of the aorta
  arch, relation between ductus arteriosus, coarctation and tubular hypoplasia, 35 specimens (Ho & Anderson). 268
  cusp, prolapsed, with vegetation, echocardiographic findings: case report (Shiu *et al.*). 118
  and mitral valve surgery, elective, over 70 years of age (Canepa-Anson & Emanuel). 493
  valve, disease, pre- and postoperative left ventricular contractile function (Krayenbuehl *et al.*). 204
    stenosis, cross-sectional echocardiographic (Davies *et al.*). 374, *P.*
    pulmonary hypertension and sudden death (McHenry *et al.*). 463
  wall echogram, posterior, evaluation in diagnosis of mitral valve disease (Hall *et al.*). 522
Apex cardiogram recorded with six different transducer systems, comparability and reproducibility (Willems *et al.*). 716
Arrhythmias
  endocardial mapping and cryosurgery for (Bentall *et al.*). 371, *P.*
  and Mustard's operation (Shinebourne *et al.*). 367, *P.*
  on and off beta-blocker therapy, ECG monitoring to assess (McKenna *et al.*). 375, *P.*
  supraventricular, amiodarone in prophylaxis (Rowland *et al.*). 372, *P.*
  ventricular, early, reduction by acebutolol in myocardial infarction (Ahumada *et al.*). 654
Atrial
  appendages, left-sided juxtaposition, disposition of sinus node in (Ho *et al.*). 129
  fibrillation, effects on prognosis of acute myocardial infarction (Loewy: Hunt). 255
  infarction leading to rupture: case report (Cristal *et al.*). 350
  septal defects, identification by cross-sectional contrast echocardiography (Bourdillon *et al.*). 382, *P.*
  situs, determination, in three cases of absent spleen with discordant anatomy between bronchi and atria (Caruso & Becker). 559
Atrioventricular
  block, chronic, prognosis of patients paced for (Ginks, *et al.*). 633
    pacemaker technology (Sutton & Citron). 600
  and ventriculo-arterial relations, gross distortion associated with left juxtaposition of atrial appendages (Coto *et al.*). 486

Baroreflex sensitivity in hypertension during beta-adrenergic blockade (Krediet & Dunning). 106
Benzoyl-indolizine (L 9394) electrophysiological effects in man (Waleffe *et al.*). 89
Beta-adrenergic blockade
  baroreflex sensitivity in hypertension during (Krediet & Dunning). 106
  and alpha-adrenergic blockade, effects on nocturnal blood pressure in hypertensives (Mann *et al.*). 384, *P.*
  ECG monitoring to assess arrhythmia on and off (McKenna *et al.*). 375, *P.*
  long-term, effects in rabbit (Evemy *et al.*). 383, *P.*
  see also Propranolol: Metoprolol
Bicarbonate infusions, oxygen administration and brief hyperventilation in pulmonary vascular obstructive disease (Morrison & Macartney). 584
Björk-Shiley mitral valve prosthesis, associated with near fatal puerperal thrombosis: correspondence (Rajah *et al.*: McLeod *et al.*,). 630
Block
  atrioventricular, chronic, prognosis of patients paced for (Ginks *et al.*). 633
  bundle-branch, complete right, echophonocardiographic study of first heart sound and right ventricular contraction times (Brooks *et al.*). 637
Blood
  pressure in infancy, epidemiological study (de Swiet *et al.*). 383, *P.*
    nocturnal, in hypertensives and effects of alpha and beta adrenergic blockade (Mann *et al.*). 384, *P.*
  volume in angina pectoris (Åström *et al.*). 477

- Bundle-branch block, right, complete, echophonocardiographic study of first heart sound and right ventricular contraction times (Brooks *et al.*). 637
- Bypass surgery
  - coronary, changes in regional myocardial lactate metabolism after (Bergman *et al.*). 369, *P.*
  - in first year of life using profound hypothermia and circulatory arrest (Di Eusanio *et al.*). 294
  - graft status after, prediction by thallium-201 exercise scintigraphy (Murray *et al.*). 369, *P.*
  - haemodynamic effects of angiotensin blockade (Taylor *et al.*). 380, *P.*

- Cardiac
  - failure, *see* Heart failure
  - rhythm in healthy newborn infant (Southall *et al.*). 382, *P.*
  - surgery, recognition and quantification of myocardial injury after by plasma enzyme and isoenzyme activities (Van Der Laarse *et al.*). 660
- Cardiomyopathic syndrome caused by coronary artery disease (Boucher *et al.*). 613
- Cardiomyopathy
  - congestive, antibodies to Coxsackie B viruses (Cambridge *et al.*). 692
  - hypertrophic, assessment of chest pain by thallium-201 myocardial scintigraphy (Pitcher *et al.*). 379, *P.*
  - obstructive and non-obstructive hypertrophic, diagnosis, role of echocardiography (Doi *et al.*). 379, *P.*
- Cardiovascular
  - drug assessment, echocardiography (Martin & Fieller). 536
  - and sympathetic adaptation with bicycle exercise (Watson *et al.*). 383, *P.*
- Catecholamines
  - concentration in human cardiac muscle (Petch & Nayler). 340
  - uptake by human cardiac muscle in vitro (Petch & Nayler). 336
- Chest pain, with coronary arteriograms, abnormal left ventricular wall movement in (Gibson & Brown). 385
- Chylopericardium, isolated primary: case report (Ross *et al.*). 508
- Clofibrate, in primary prevention of ischaemic heart disease (Oliver). 363, *P.*
- Coarctation of the aorta
  - associated with Marfanoid hypermobility syndrome: case report (Daneshwar *et al.*). 621
  - tubular hypoplasia and ductus arteriosus, relation between, 35 specimens (Ho & Anderson). 268, 361, *P.*
  - tubular, hypoplasia and ductus arteriosus: histological study (Ho & Anderson). 361, *P.*
- Congenital heart disease, nomenclature and classification (Tynan *et al.*). 544
- Congestive cardiomyopathy, *see* Cardiomyopathy, congestive
- Core cooling (profound hypothermia and circulatory arrest in open heart surgery in first year of life (Di Eusanio *et al.*). 294
- Coronary
  - artery, left, anomalous origin, successful surgical correction: case report (Hamilton *et al.*). 121
    - bypass surgery, in angina pectoris, multicentre prospective randomised study, survival at 2 years (Varnauskas). 363, *P.*
      - objective non-invasive assessment (Fox *et al.*). 368, *P.*
      - *see also* Bypass surgery
    - vasospasm, likely immediate cause of acute myocardial infarction (Hellstrom). 426
  - care unit, mobile, measuring effect on community (Vetter *et al.*). 418
    - patients treated in without acute myocardial infarction, identification of high risk subgroup (Nordlander & Nyquist). 647
    - thallium-201 scintigraphy in selection of patients (Wackers *et al.*). 111
  - collateral circulation during dynamic exercise evaluated by thallium-201 myocardial scintigraphy (Wainwright). 360, *P.*
  - heart disease, during atrial pacing, left ventricular ejection power (Hagemann *et al.*). 231
    - causing cardiomyopathic syndrome (Boucher *et al.*). 613
    - changes in form and function (Somerville). 1
    - cyanotic, haemostatic defects (Henriksson *et al.*). 23
    - influence of cigarette smoking on morbidity, mortality and mode of death (Mulcahy *et al.*). 365, *P.*
    - lung biopsy (Haworth *et al.*). 362, *P.*
    - pattern of disturbed myocardial perfusion in (Oakley *et al.*). 376, *P.*
    - prevalence in black schoolchildren, Soweto (McLaren *et al.*). 554
    - quantification (Roberts). 363, *P.*
    - severe, 12-lead maximal exercise testing as predictor (Baron *et al.*). 364, *P.*
    - thallium-201 scintigraphy in evaluation (Murray *et al.*). 568
      - comparison with other methods (Corne *et al.*). 575
- Correspondence
  - Echocardiographic identification of aorta and main pulmonary artery in complete transposition (Satomi *et al.*: Houston *et al.*). 356, (Daniëls: Houston *et al.*). 631
  - Effects of atrial fibrillation on prognosis of acute myocardial infarction (Loewy: Hunt). 255
  - Near fatal puerperal thrombosis on Björk-Shiley mitral valve prosthesis (Rajah *et al.*: McLeod *et al.*). 630
  - Severe complication of pulmonary vein angiography (Singh & Astley). 740
  - Systolic time intervals and impedance cardiography (Spodick: Balasubramanian). 253
- Counterpulsation, arterial, in severe refractory heart failure complicating acute myocardial infarction (O'Rourke *et al.*). 308
- Coxsackie B viruses, antibodies in congestive cardiomyopathy (Cambridge *et al.*). 692
- Creatine kinase release and infarct size and ejection fraction correlation, myocardial infarction (Hori *et al.*). 433
- Cryosurgery and endocardial mapping for arrhythmias (Bentall *et al.*). 371, *P.*
- Cyanotic congenital heart disease, haemostatic defects (Henriksson *et al.*). 23

- Death, sudden
  - during marathon racing, associated with hypertrophic cardiomyopathy: case report (Noakes *et al.*). 624
  - and pulmonary hypertension in aortic stenosis (McHenry *et al.*). 463
- Defibrillation, ventricular (Patton). 361, *P.*
- Diabetes, Valsalva manoeuvre, left ventricular response using praecordial accelerocardiography (Hume *et al.*). 199
- Dizziness, dynamic ECGs in 405 patients (Wang *et al.*). 373, *P.*
- Doerr's theory of morphogenesis of arterial transposition (Chuaqui). 481
- Doppler echocardiography in determination of pressure gradient in mitral stenosis (Holen & Simonsen). 529
- Double outlet right ventricle with subvalvular aortic stenosis: case report (Thanopoulos *et al.*). 241
- Drugs, cardiovascular, echocardiography in assessment (Martin & Fieller). 536
- Ductus arteriosus, persistent
  - failure of indomethacin to close, in infants under 1000 grams (Ivey *et al.*). 304
  - poor response to oral indomethacin therapy in very low

    birthweight infants (Cooke & Pickering). 301
  tubular hypoplasia and coarctation, relation between, 35 specimens (Ho & Anderson). 268, 361, *P.*

Ebstein's anomaly of tricuspid valve and corrected transposition of great vessels, echocardiography: case report (Henry *et al.*). 249
Echocardiography
  in anomalous systemic and coronary venous return (Foale *et al.*). 381, *P.*
  cross-sectional contrast, in identification of atrial septal defects (Bourdillon *et al.*). 382, *P.*
  in diagnosis of obstructive and non-obstructive hypertrophic cardiomyopathy (Doi *et al.*). 379, *P.*
  Doppler, in determination of pressure gradient in mitral stenosis (Holen & Simonsen). 529
  identification of aorta and main pulmonary artery in complete transposition: correspondence (Daniëls: Houston *et al.*). 631
  phased-array, in study of rotational excursion of heart in massive pericardial effusion (Matsuo *et al.*). 513
Editorial: Thyroid heart disease (Symons). 257
Ejection fraction and infarct size estimated from total CK released, myocardial infarction (Hori *et al.*). 433
Electrocardiograms
  dynamic, value in 405 patients with dizziness, syncope, or palpitation (Wang *et al.*). 373, *P.*
  ischaemic-like, in asymptomatic men, studies with atrial pacing, adrenaline infusion and autonomic blockade (Taggart *et al.*). 376, *P.*
  12-lead maximal exercise testing as predictor of severe coronary artery disease (Baron *et al.*). 364, *P.*
Enzyme, plasma, determination after cardiac surgery in recognition and quantification of myocardial injury (Van Der Laarse *et al.*). 660
Ergometrine in predicting vasospastic angina, value and limitation (Rothman *et al.*). 370, *P.*
Exercise
  bicycle, cardiovascular and sympathetic adaptation (Watson *et al.*). 383, *P.*
  maximal, computer processed thallium-201 scintigrams during and 4 hours after (Layton & Stockley). 368, *P.*
  maximal supine haemodynamics after open heart surgery for Fallot's tetralogy (Cumming). 683
  testing and ambulatory ECG monitoring after surgical repair of Fallot's tetralogy and ventricular septal defect (Irving & Godman). 368, *P.*
  thallium-201 scintigraphy evaluation (Murray). 360, P: (Wainwright). 360, *P.*

Fallot's tetralogy
  before and after surgery, echocardiographical study of right and left ventricular dimension and function (Oberhänsli & Friedli). 40
  postoperative haemodynamics, 132 children (Joransen *et al.*). 33
Fibrinolytic activity on Monday and on other days (Meade *et al.*). 375, *P.*
Finite element method in analysis of left ventricular behaviour in diastole (Vinson *et al.*). 60
Fontan operation and its modification, indications and results (O'Riordan *et al.*). 366, *P.*

Glyceryl trinitrate
  paste inducing pulsus alternans in alcoholic cardiomyopathy: case report (Chandraratna *et al.*). 354
  vs post-ectopic potentiation in assessment of ischaemic left ventricle (Rickards *et al.*). 377, *P.*
Graft status after bypass surgery, prediction by thallium-201 exercise scintigraphy (Murray *et al.*). 369, *P.*

Hancock porcine xenograft valve prosthesis, early clinical experience (Sang *et al.*). 226
Heart
  angiosarcoma (Shackell *et al.*). 498
  block, complete, and polymyositis: case report (Reid & Murdoch). 628
  failure, congestive, haemodynamic effects of sodium nitroprusside (Lukes *et al.*). 187
  salbutamol treatment (Poole-Wilson *et al.*). 380, *P.*
      and isosorbide dinitrate alone and in combination in (Stephens *et al.*). 381, *P.*
    refractory congestive, comparative effects of oral and chewable isosorbide dinitrate (Figueras *et al.*). 317
    severe refractory, arterial counterpulsation in complicating acute myocardial infarction (O'Rourke *et al.*). 308
  size and function in acromegaly (Mather *et al.*). 697
Homograft aortic valve replacement, fresh unstented, 8 years experience (Thompson *et al.*). 374, *P.*
Hydralazine in impaired left ventricular function haemodynamic effects at rest and during exercise (Ginks & Redwood). 381, *P.*
Hypertension
  baroreflex sensitivity during beta-adrenergic blockade (Krediet & Dunning). 106
  labetalol treatment, haemodynamic adaptation at rest and during exercise (Koch). 192
  effects of propranolol and metoprolol during exercise (Van Herwaarden *et al.*). 99
  pulmonary, primary, long-term follow-up (Suarez *et al.*). 702
    and sudden death in aortic stenosis (McHenry *et al.*). 463
    vascular disease, lung scan abnormalities (MacArthur *et al.*). 362, *P.*
Hypertrophic cardiomyopathy associated with sudden death during marathon racing: case report (Noakes *et al.*). 624
Hypertrophy, left ventricular, secondary, echocardiographic features (Gibson *et al.*). 54
Hyperventilation, brief, oxygen administration and bicarbonate infusions in pulmonary vascular obstructive disease (Morrison & Macartney). 584
Hypotension, orthostatic, propranolol in, case report (Brevetti *et al.*). 245
Hypothermia, profound (core cooling) and circulatory arrest in open heart surgery in first year of life (Di Eusanio *et al.*). 294

Impedance cardiography and systolic time intervals: correspondence (Spodick & Balasubramanian). 253
Indomethacin therapy, oral, for persistent ductus arteriosus in very low birthweight infants (Cooke & Pickering). 301: (Ivey *et al.*). 304
Infarct size and ejection fraction, correlation estimated from total CK released, myocardial infarction (Hori *et al.*). 433
Infundibular right ventricular outflow tract obstruction, non-invasive diagnosis (Mills *et al.*). 382, *P.*
Ischaemia, myocardial, in ambulatory patients with daily chest pain, assessment (Selwyn *et al.*). 376, *P.*
Ischaemic heart disease
  fibrinolytic activity on Monday and on other days (Meade *et al.*). 375, *P.*
  primary prevention using clofibrate, co-operative trial (Oliver *et al.*). 363, *P.*
Isosorbide dinitrate
  oral and chewable, comparative effects in refractory congestive cardiac failure (Figueras *et al.*). 317
  and oral salbutamol, alone and in combination in severe chronic congestive cardiac failure (Stephens *et al.*). 381, *P.*
Isovolumic relaxation, relation to left ventricular wall movement in man (Chen & Gibson). 377, *P.*

Jones, A. Morgan, Obituary. 738

L 9394 (benzoyl-indolizine) electrophysiological effects in man (Waleffe *et al.*). 89
Labetalol, in hypertensive treatment, haemodynamic adaptation at rest and during exercise (Koch). 192
Lactate metabolism, myocardial, changes after coronary bypass surgery (Bergman *et al.*). 369, *P.*
Libman-Sacks endocarditis, mitral valve replacement for mitral stenosis caused by: case report (Vaughton *et al.*). 730
Lung
  biopsy in congenital heart disease (Haworth *et al.*). 362, *P.*
  scan abnormalities in hypertensive pulmonary vascular disease (MacArthur *et al.*). 362, *P.*

Mapping, endocardial, and cryosurgery for arrhythmias (Bentall *et al.*). 371, *P.*
Marathon racing, sudden death during associated with hypertrophic cardiomyopathy: case report (Noakes *et al.*). 624
Marfanoid hypermobility syndrome associated with coarctation of the aorta: case report (Daneshwar *et al.*). 621
Metoprolol and propranolol, effects on haemodynamic and respiratory indices and on perceived exertion during exercise in hypertensive patients (Van Herwaarden *et al.*). 99
Mexiletine, haemodynamic effects (Campbell *et al.*). 182
Mitral
  and aortic valve surgery, elective, over 70 years of age (Canepa-Anson & Emanuel). 493
  valve disease, evaluation of posterior aortic wall echogram in diagnosis (Hall *et al.*). 522
    prosthesis, Björk-Shiley, associated with near fatal puerperal thrombosis: correspondence (Rajah *et al.*: McLeod *et al.*). 630
    replacement for mitral stenosis caused by Libman-Sacks endocarditis (Vaughton *et al.*). 730
      porcine heterograft, in mitral position, clinical and haemodynamic evaluation (Cotter & Miller). 412
    regurgitation, correlation of echocardiographic, surgical, and pathological findings (Mills *et al.*). 374, *P.*
    stenosis caused by Libman-Sacks endocarditis, mitral valve replacement (Vaughton *et al.*). 730
    determination of pressure gradient with Doppler echocardiography (Holen & Simonsen). 529
    with high left ventricular diastolic pressure (Traill *et al.*). 405
    posterior leaflet movement, after mitral valve repair (Thomas *et al.*). 399
  valvotomy, echocardiographic and exercise evaluation of results (Shiu *et al.*). 139
Morgan Jones, A. Obituary. 738
Mustard's operation and arrhythmias (Shinebourne *et al.*). 367, *P.*
Myocardial
  infarct size, estimation using 99m Tc polyphosphate (Davies *et al.*). 668
  infarction, arterial counterpulsation in severe refractory heart failure complicating (O'Rourke *et al.*). 308
    atrial fibrillation, effects on prognosis: correspondence (Loewy: Hunt). 255
    cigarette smoking, influence on morbidity, mortality, and mode of death (Mulcahy *et al.*). 365, *P.*
    coronary artery vasospasm as likely cause (Hellstrom). 426
    ejection fraction and infarct size estimated from total CK released (Hori *et al.*). 433
    multicentre propranolol post-infarction trial (Baber *et al.*). 365, *P.*
    normalisation of ECG after treatment with beta-blockers (Yusuf *et al.*). 364, *P.*
    QT time after treatment with alprenolol or placebo (Nyberg *et al.*). 452
    reduction of early ventricular arrhythmia by acebutolol in (Ahumada *et al.*). 654
    serum myoglobin determination in diagnosis and quantitation (Maddison *et al.*). 370, *P.*
    wall motion abnormalities in, and biplane radionuclide ventriculography (Dymond *et al.*). 378, *P.*
  injury, plasma enzyme determinations to determine after cardiac surgery (Van Der Laarse *et al.*). 660
  ischaemia, electrocardiographic changes resembling in asymptomatic men with normal coronary arteriograms (Taggart *et al.*). 214
  perfusion, regional, pattern of disturbance in coronary artery disease (Oakley *et al.*). 376, *P.*

Nitroprusside infusion, left ventricular pressure-volume relations during, without coronary artery disease (Merillon *et al.*). 325
Nocardia asteroides causing prosthetic valve endocarditis: case report (Falk *et al.*). 125
Notices 128, 256, 398, 512, 632

Obituary: Arthur Morgan Jones (Wade). 738
Open heart surgery
  for Fallot's tetralogy, maximal supine exercise haemodynamics after (Cumming). 683
  in first year of life, using profound hypothermia and circulatory arrest (Di Eusanio *et al.*). 294
Outflow tract
  left ventricular, anatomy (Walmsley). 263
  ventricular, obstruction, and ventricular septal thickening (Maron *et al.*). 345
Oxygen administration, bicarbonate infusions and brief hyperventilation in pulmonary vascular obstructive disease (Morrison & Macartney). 584

Pacemaker technology in sick sinus syndrome and atrioventricular block (Sutton & Citron). 600
Pacing
  atrial, coronary artery disease during, left ventricular ejection power (Hagemann *et al.*). 231
  electrodes, temporary and permanent, comparison with strength-interval curves (Mehra & Furman). 468
Palpitation, dynamic ECGs in 405 patients (Wang *et al.*). 373, *P.*
Pericardial effusion, massive, rotational excursion of heart, phased-array echocardiography (Matsuo *et al.*). 513
Phenylephrine and sodium nitroprusside, effects on coronary dynamics with normal left ventricular function (Stephens *et al.*). 456
Polymyositis and complete heart block: case report (Reid & Murdoch). 628
Pompe's disease (glycogenosis type II) unusual appearances of left ventricle (Dickinson *et al.*). 238
Porcine
  heterograft mitral valve replacement, in mitral position, clinical and haemodynamic evaluation (Cotter & Miller). 412
  xenograft valve prosthesis, early clinical experience (Sang *et al.*). 226
Post-ectopic potentiation vs glyceryl trinitrate in assessment of ischaemic left ventricle (Rickards *et al.*). 377, *P.*
Posterior leaflet movement, mitral valve, after mitral valve repair (Thomas *et al.*). 399
Postpartum cardiac failure syndrome of northern Nigeria, left ventricular function in (Sanderson *et al.*). 378, *P.*
Praecordial projection of ST segment changes after exercise and coronary angiography, relation between (Fox). 361, *P.*

Proceedings, British Cardiac Society, Autumn meeting, Wembley, 20 and 21 November 1978. 360
Propranolol
  clinical electrophysiological effects on normal sinus node function (Vasquez *et al.*). 709
  low dose, blockade of cardiac and renal beta-receptors in normal subjects, antihypertensive effect (Davies *et al.*). 331
  and metoprolol, effects on haemodynamic and respiratory indices and on perceived exertion during exercise in hypertensive patients (Van Herwaarden *et al.*). 99
  multicentre, post-infarction trial (Baber *et al.*). 365, *P.*
  in orthostatic hypotension: case report (Brevetti *et al.*). 245
Pulmonary
  atresia, morphological variations with intact ventricular septum (Zuberbuhler & Anderson). 281
  vascular obstructive disease, effects of oxygen administration, bicarbonate infusions, and brief hyperventilation (Morrison & Macartney). 584
  vein angiography, severe complication: case report (Alpert & Culham). 727: correspondence (Singh & Astley). 740
Pulsus alternans induced by glyceryl trinitrate paste in alcoholic cardiomyopathy: case report (Chandraratna *et al.*). 354

QT time, alprenolol treatment or placebo in myocardial infarction (Nyberg *et al.*). 452

Radionuclide ventriculography in detection of postinfarction left ventricular aneurysms (Dymond *et al.*). 68
Rotational excursion of heart, massive pericardial effusion, phased-array echocardiography (Matsuo *et al.*). 513

Salbutamol in heart failure (Poole-Wilson *et al.*). 380, *P.*
  and isosorbide dinitrate, alone or in combination in severe chronic congestive cardiac failure (Stephens *et al.*). 381, *P.*
Sarcoid heart disease in UK (Fleming). 379, *P.*
Scintigraphy
  gated blood pool, limitations, clinical and experimental aspects (Walton *et al.*). 373, *P.*
  thallium-201, in assessment of chest pain in hypertrophic cardiomyopathy (Pitcher *et al.*). 379, *P.*
    computer processed during and 4 hours after maximal exercise (Layton & Stockley). 368, *P.*
    in coronary collateral circulation, evaluation during exercise (Wainwright). 360, *P.*
    in coronary heart disease evaluation (Murray *et al.*). 568
    in coronary stenosis diagnosis, comparison with other methods (Corne *et al.*). 575
    exercise, analysis (Murray). 360, *P.*: (Wainwright). 360, *P.*
    exercise in predicting coronary artery graft status (Murray *et al.*). 369, *P.*
    in selecting patients for coronary care unit (Wackers *et al.*). 111
Septal defect, ventricular
  changes in form and function (Somerville). 1
  conduction disturbances after surgical correction by atrial approach (Hobbins *et al.*). 289
Septum, ventricular, thickening, and outflow obstruction (Maron *et al.*). 345
Sick sinus syndrome, pacemaker technology (Sutton & Citron). 600
Sinus node
  disease in young people (Mackintosh). 372, *P.*
  disposition in left-sided juxtaposition of atrial appendages (Ho *et al.*). 129
  dysfunction associated with absence of right superior vena cava: case report (Camm *et al.*). 504
  function, clinical electrophysiological effects of propranolol on (Vasquez *et al.*). 709
  in human heart, location and vascular supply (Anderson *et al.*). 28
Smoking, cigarette, influence on morbidity, mortality, and mode of death in coronary patients (Mulcahy *et al.*). 365, *P.*
Sodium nitroprusside
  in congestive heart failure, haemodynamic effects (Lukes *et al.*). 187
  and phenylephrine, effects on coronary dynamics with normal left ventricular function (Stephens *et al.*). 456
Stenosis, aortic, critical, in early infancy (Silove *et al.*). 367, *P.*
  mitral, *see* Mitral stenosis
  subaortic, *see* Subaortic
  subvalvular, *see* Subvalvular
Strength-interval curves, comparison of cathodal, anodal, and bipolar, with temporary and permanent pacing electrodes (Mehra & Furman). 468
  stenosis, fixed, echocardiography in diagnosis and differentiation (Ten Cate *et al.*). 159
    fixed (discrete)—late results of resection, congenital or acquired lesion (Somerville). 366, *P.*
Subvalvular aortic stenosis with double outlet right ventricle: case report (Thanopoulos *et al.*). 241
Sympathetic and cardiovascular adaptation with bicycle exercise (Watson *et al.*). 383, *P.*
Syncope, dynamic ECGs in 405 patients (Wang *et al.*). 373, *P.*
Systolic time intervals and impedance cardiography: correspondence (Spodick: Balasubramanian). 253

Tachycardia
  alternating atrial and ventricular: case report (Jordan *et al.*). 734
  control by long-term programmed stimulation (Kappenberger & Sowton). 371, *P.*
Technetium-99m labelled cardiac blood pool, multiple gated acquisition on in assessment of ventricular function (Wainwright *et al.*). 378, *P.*
Technetium stannous polyphosphate, 99m, in estimation of myocardial infarct size (Davies *et al.*). 668
Tetralogy of Fallot, *see* Fallot's tetralogy
Thallium-201 scintigraphy, *see* Scintigraphy
Thrombosis, puerperal, near fatal, on Björk-Shiley mitral valve prosthesis: correspondence (Rajah *et al.*: McLeod *et al.*). 630
Thyroid heart disease: editorial (Symons). 257
Tocainide, effects on left ventricular performance, echocardiography (Ryan & Karliner). 175
Transposition of great vessels
  corrected, and Ebstein's anomaly of tricuspid valve, echocardiography: case report (Henry *et al.*). 249
  complete, echocardiographic identification of aorta and main pulmonary artery in: correspondence (Daniëls: Houston *et al.*). 631
    echocardiographic identification of aorta and main pulmonary artery (Satomi *et al.*: Houston *et al.*). 356
  Doerr's theory of morphogenesis (Chuaqui). 481
  with intact ventricular septum and left ventricular outflow tract obstruction: management (Crupi *et al.*). 366, *P.*
Tricuspid atresia, early and late problems after pulmonary artery to right atrial connection (Osnaya & Somerville). 365, *P.*
Tubular hypoplasia, coarctation and ductus arteriosus, relation between, 35 specimens (Ho & Anderson). 268, 361, *P.*

Uhl's anomaly (Vecht *et al.*). 676

- Valsalva manoeuvre, in normal and diabetic subjects, non-invasive assessment of left ventricular response using praecordial accelerocardiography (Hume *et al.*). 199
- Valve
  - aortic, use of fresh unstented homograft replacements, 8 years experience (Thompson *et al.*). 374, *P.*
  - prosthetic, endocarditis resulting from *Nocardia asteroides*: case report (Falk *et al.*). 125
    - porcine xenograft, early clinical experience (Sang *et al.*). 226
    - *see also* Aortic: Mitral
- Vena cava, right superior, absence, sinus node dysfunction associated with: case report (Camm *et al.*). 504
- Veno-occlusive disease of the liver, haemodynamic studies (Kasturi *et al.*). 594
- Venous return, anomalous systemic and coronary, echocardiographic features (Foale *et al.*). 381, *P.*
- Verapamil, in unstable angina at rest (Parodi *et al.*). 167
- Ventricle (ventricular)
  - arrhythmia, early, reduction by acebutolol in myocardial infarction (Ahumada *et al.*). 654
  - defibrillation (Patton). 361, *P.*
  - dimension and function before and after surgery for Fallot's tetralogy, echocardiography (Oberhänsli & Friedli). 40
  - ectopy, differentiation from aberration (Talbot *et al.*). 372, *P.*
  - function, assessment by gated blood pool scintigraphy (Walton *et al.*). 373, *P.*
    - in response to cold pressor test: MUGA-99Tcm (Wainwright *et al.*). 378, *P.*
  - left, analysis of behaviour in diastole by means of finite element method (Vinson *et al.*). 60
    - aneurysms, postinfarction, detection by radionuclide ventriculography (Dymond *et al.*). 68
    - ejection power in coronary artery disease during atrial pacing (Hagemann *et al.*). 231
    - function, failure of aneurysmectomy to improve (Sesto *et al.*). 79
      - hydralazine in, haemodynamic effects at rest and during exercise (Ginks & Redwood). 381, *P.*
      - in postpartum cardiac failure syndrome of northern Nigeria (Sanderson *et al.*). 378, *P.*
    - high diastolic pressure in mitral stenosis (Traill *et al.*). 405
    - hypertrophy, secondary, echocardiographic features (Gibson *et al.*). 54
    - ischaemic, glyceryl trinitrate vs post-ectopic potentiation in assessment (Rickards *et al.*). 377, *P.*
    - ischaemia, patterns of haemodynamic alteration (Johnson *et al.*). 441
    - minor axis shortening during pre-ejection phase of systole, echocardiography (Chandraratna *et al.*). 392
    - outflow tract, anatomy (Walmsley). 263
    - in Pompe's disease (glycogenosis type II) unusual angiographic appearances (Dickinson *et al.*). 238
    - pressure-volume relations during nitroprusside infusion without coronary artery disease (Merillon *et al.*). 325
  - right, inlet zone, development, man (Anderson *et al.*). 362, *P.*
  - septum, defect, assessment of left-to-right shunt and left ventricular function, echocardiography (Ahmad & Hallidie-Smith). 147
      - conduction disturbances after surgical correction by atrial approach (Hobbins *et al.*). 289
      - changes in form and function (Somerville). 1
      - surgical treatment in infancy, primary repair versus banding of pulmonary artery and later repair (McNicholas *et al.*). 133
    - intact, morphological variations in pulmonary atresia (Zuberbuhler & Anderson). 281
    - membranous part, developmental anatomy (Allwork & Anderson). 275
    - thickening, nongenetically transmitted disproportionate, associated with left ventricular outflow obstruction (Maron *et al.*). 345
  - wall, movement, left, abnormal, in chest pain and normal coronary arteriograms (Gibson & Brown). 385
      - left, relation of isovolumic relaxation to (Chen & Gibson) 377, *P.*
- Ventriculo-arterial and atrioventricular relations, gross distortion associated with left juxtaposition of atrial appendages (Coto *et al.*). 486
- Ventriculography
  - biplane first pass radionuclide, in assessment of wall motion abnormalities in myocardial infarction (Dymond *et al.*). 378, *P.*
  - quantitative, automated system (Brunt *et al.*). 373, *P.*
  - radionuclide, in detection of postinfarction left ventricular aneurysms (Dymond *et al.*). 68

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CONTENTS OF VOLUME 41

Number 1

page

Congenital Heart Disease—Changes in Form and Function Jane Somerville 1

Haemostatic Defects in Cyanotic Congenital Heart Disease
P. Henriksson, Gunilla Värendh, and N.-R. Lundström 23

Location and Vascular Supply of Sinus Node in Human Heart
K. R. Anderson, S. Yen Ho, and R. H. Anderson 28

Postoperative Haemodynamics in Tetralogy of Fallot. A Study of 132 Children
J. A. Joransen, R. V. Lucas, Jr., and J. H. Moller 33

Echocardiographic Study of Right and Left Ventricular Dimension and left Ventricular Function in Patients with Tetralogy of Fallot Before and After Surgery
I. Oberhänsli and B. Friedli 40

Echocardiographic Features of Secondary Left Ventricular Hypertrophy
D. G. Gibson, T. A. Traill, R. J. C. Hall, and D. J. Brown 54

Analysis of Left Ventricular Behaviour in Diastole by Means of Finite Element Method
C. A. Vinson, D. G. Gibson, and A. L. Yettram 60

Detection of Postinfarction Left Ventricular Aneurysms by First Pass Radionuclide Ventriculography Using a Multicrystal Gamma Camera
D. S. Dymond, P. H. Jarritt, K. E. Britton, and R. A. J. Spurrell 68

Failure of Aneurysmectomy to Improve Left Ventricular Function
M. Sesto, F. Schwarz, K.-U. Thiedemann, W. Flameng, and M. Schlepper 79

Electrophysiological Effects of L 9394 (Benzoylindolizine) In Man
A. Waleffe, A. Bordalo, P. Bruninx, H. J. J. Wellens, and H. E. Kulbertus 89

Effects of Propranolol and Metoprolol on Haemodynamic and Respiratory Indices and on Perceived Exertion During Exercise in Hypertensive Patients
C. L. A. van Herwaarden, R. A. Binkhorst, J. F. M. Fennis, and A. van't Laar 99

Baroreflex Sensitivity in Hypertension During Beta-Adrenergic Blockade
R. T. Krediet and A. J. Dunning 106

Potential Value of Thallium-201 Scintigraphy as a Means of Selecting Patients for the Coronary Care Unit
F. J. Th. Wackers, K. I. Lie, K. L. Liem, Ellinor Busemann Sokole, G. Samson, Jan van der Schoot, and D. Durrer 111

Case Reports 118, 121, 125

Notices 128

Number 2

Disposition of the Sinus Node in Left-Sided Juxtaposition of the Atrial Appendages
S. Yen Ho, J. L. Monro and R. H. Anderson 129

Surgical Treatment of Ventricular Septal Defect in Infancy. Primary Repair Versus Banding of Pulmonary Artery and Later Repair
K. McNicholas, M de Leval, J. Stark, J. F. N. Taylor, and F. J. McCartney 133

Echocardiographic and Exercise Evaluation of Results of Mitral Valvotomy Operations
M. F. Shiu, A. Crowther, B. S. Jenkins, and M. M. Webb Peploe 139

Assessment of Left-to-Right Shunt and Left Ventricular Function in Isolated Ventricular Septal Defect. Echocardiographic Study M. Ahmad and K. A. Hallidie-Smith 147

Fixed Subaortic Stenosis. Value of Echocardiography for Diagnosis and Differentiation Between Various Types F. J. Ten Cate, W. G. Van Dorp, P. G. Hugenholtz, and J. Roelandt 159

Management of Unstable Angina at Rest by Verapamil. A Double-Blind Cross-Over Study in Coronary Care Unit O. Parodi, A. Maseri, and I. Simonetti 167

Effects of Tocainide on Left Ventricular Performance at Rest and During Acute Alterations in Heart Rate and Systemic Arterial Pressure. An Echocardiograhpic Study
W. F. Ryan and J. S. Karliner 175

Observations on Haemodynamic Effects of Mexiletine
N. P. S. Campbell, S. A. Zaidi, A. A. J. Adgey, G. C. Patterson, and J. F. Pantridge 182

Number 2—*(continued)*

page

Haemodynamic Effects of Sodium Nitroprusside in 21 Subjects with Congestive Heart Failure S. A. Lukes, C. A. Romero, Jr., and L. Resnekov 187

Haemodynamic Adaptation at Rest and During Exercise to Long-Term Antihypertensive Treatment with Combined Alpha- and Beta- Adronoreceptor Blockade by Labetalol G. Koch 192

Non-Invasive Assessment of Left Ventricular Response to Valsalva Manoeuvre in Normal and Diabetic Subjects Using Praecordial Accelerocardiography L. Hume, D. J. Ewing, I. W. Campbell, S. R. Reuben, and B. F. Clarke 199

Pre- and Postoperative Left Ventricular Contractile Function in Patients with Aortic Valve Disease H. P. Krayenbuehl, M. Turina, O. M. Hess, M. Rothlin, and A. Senning 204

Electrocardiographic Changes Resembling Myocardial Ischaemia in Asymptomatic Men with Normal Coronary Arteriograms P. Taggart, M. Carruthers, S. Joseph, H. B. Kelly, J. Marcomichelakis, D. Noble, G. O'Neill, and W. Somerville 214

Early Clinical Experience with the Hancock Porcine Xenograft Valve Prosthesis C. T. M. Sang, J. Wallwork, H. C. Miller, A. H. Kitchin, K. G. Davidson, and P. K. Caves 226

Left Ventricular Ejection Power in Coronary Artery Disease During Atrial Pacing K. Hagemann, J. Meyer, R. v. Essen, Winifried Krebs, and S. Effert 231

Unusual Angiographic Appearances of the Left Ventricle in 2 Cases of Pompe's Disease (Glycogenosis Type II) D. F. Dickinson, W. T. Houlsby, and J. L. Wilkinson 238

Case Reports 241, 245, 249

Correspondence 253

Notices 256

Number 3

Editorial: Thyroid Heart Disease Cecil Symons 257

Anatomy of Left Ventricular Outflow Tract Robert Walmsley 263

Coarctation, Tubular Hypoplasia, and the Ductus Arteriosus. Histological Study of 35 Specimens S. Yen Ho and Robert H. Anderson 268

Developmental Anatomy of the Membranous Part of the Ventricular Septum in the Human Heart S. P. Allwork and R. H. Anderson 275

Morphological Variations in Pulmonary Atresia with Intact Ventricular Septum James R. Zuberbuhler and Robert H. Anderson 281

Conduction Disturbances After Surgical Correction of Ventricular Septal Defect by the Atrial Approach Susan M. Hobbins, Teruo Izukawa, Dorothy J. Radford, William G. Williams, and George A. Trusler 289

Open Heart Surgery in First Year of Life Using Profound Hypothermia (Core Cooling) and Circulatory Arrest. Experience with 134 Consecutive Cases Giuseppe Di Eusanio, Sadhan C. Ray, Raymund J. Donnelly, and David I. Hamilton 294

Poor Response to Oral Indomethacin Therapy for Persistent Ductus Arteriosus in Very Low Birthweight Infants Richard W. I. Cooke and Douglas Pickering 301

Failure of Indomethacin to Close Persistent Ductus Arteriosus in Infants Weighing Under 1000 Grams Hallam H. Ivey, John Kattwinkel, Tong S. Park, and L. Jerome Krovetz 304

Arterial Counterpulsation in Severe Refractory Heart Failure Complicating Acute Myocardial Infarction Michael F. O'Rourke, Neville Sammel, and Victor P. Chang 308

Comparative Haemodynamic and Peripheral Vasodilator Effects of Oral and Chewable Isosorbide Dinitrate in Patients with Refractory Congestive Cardiac Failure Jaime Figueras, William R. Taylor, Takeshi Ogawa, James S. Forrester, Bramah N. Singh, and H. J. C. Swan 317

Study of Left Ventricular Pressure-Volume Relations During Nitroprusside Infusion in Human Subjects Without Coronary Artery Disease J. P. Merillon, G. Motte, M. C. Aumont, R. Prasquier, and R. Gourgon 325

Number 3—*(continued)*

page

Blockade of Cardiac and Renal Beta-Receptors by Low Dose Propranolol in Normal Subjects. Clues to its Antihypertensive Effect
Roy Davies, Thomas G. Pickering, Alberto Morganti, Maxim Wilson, and John H. Laragh 331

Uptake of Catecholamines by Human Cardiac Muscle In Vitro
M. C. Petch and W. G. Nayler 336

Concentration of Catecholamines in Human Cardiac Muscle
M. C. Petch and W. G. Nayler 340

Nongenetically Transmitted Disproportionate Ventricular Septal Thickening Associated with Left Ventricular Outflow Obstruction
Barry J. Maron, John S. Gottdiener, William C. Roberts, William J. Hammer, and Stephen E. Epstein 345

Case Reports 350, 354

Correspondence 356

Proceedings of the British Cardiac Society 360

Number 4

Abnormal Left Ventricular Wall Movement in Patients with Chest Pain and Normal Coronary Arteriograms. Relation to Inferior T Wave Changes and Mitral Prolapse
D. G. Gibson and D. J. Brown 385

Echocardiographic Study of Significance of Left Ventricular Minor Axis Shortening During Pre-ejection Phase of Systole
P. A. N. Chandraratna, G. Vlahovich, and W. S. Aronow 392

Echocardiographic Pattern of Posterior Mitral Valve Leaflet Movement After Mitral Valve Repair
R. D. Thomas, D. A. S. Mary, and M. I. Ionescu 399

Mitral Stenosis with High Left Ventricular Diastolic Pressure
T. A. Traill, M. G. St. John Sutton, and D. G. Gibson 405

Clinical and Haemodynamic Evaluation of Mounted Porcine Heterograft in Mitral Position
L. Cotter, and Hugh C. Miller 412

Measuring the Effect of a Mobile Coronary Care Unit Upon the Community
N. J. Vetter, S. Pocock, and D. G. Julian 418

Coronary Artery Vasospasm: The Likely Immediate Cause of Acute Myocardial Infarction
H. Richard Hellstrom 426

Correlation of Ejection Fraction and Infarct Size Estimated from the Total CK Released in Patients with Acute Myocardial Infarction
M. Hori, M. Inoue, S. Fukui, T. Shimazu, M. Mishima, N. Ohgitani, T. Minamino, and H. Abe 433

Patterns of Haemodynamic Alteration During Left Ventricular Ischaemia in Man. Relation to Angiographic Extent of Coronary Artery Disease
R. A. Johnson, L. M. Zir, R. W. Harper, R. C. Leinbach, A. M. Hutter, jun, G. M. Pohost, P. C. Block, and H. K. Gold 441

QT Time in Patients Treated with Alprenolol or Placebo After Myocardial Infarction
G. Nyberg, A. Vedin, and C. Wilhelmsson 452

Effects of Sodium Nitroprusside and Phenylephrine on Coronary Dynamics in Patients with Normal Left Ventricular Function
J. D. Stephens, R. P. Hayward, D. S. Dymond, H. Ead, L. Adams, and R. A. J. Spurrell 456

Pulmonary Hypertension and Sudden Death in Aortic Stenosis
M. M. McHenry, J. Rice, H. J. Matlof, and M. D. Flamm, jun. 463

Comparison of Cathodal, Anodal, and Bipolar Strength-Interval Curves with Temporary and Permanent Pacing Electrodes
Rahul Mehra and Seymour Furman 468

Blood Volume in Angina Pectoris
H. Åström, and B. Jonsson 477

Doerr's Theory of Morphogenesis of Arterial Transposition in Light of Recent Research
Benedicto Chuaqui 481

Gross Distortion of Atrioventricular and Ventriculoarterial Relations Associated with Left Juxtaposition of Atrial Appendages. Bizarre Form of Atrioventricular Criss-Cross
E. Otero Coto, J. L. Wilkinson, D. F. Dickinson, J. J. Rufilanchas, and J. Márquez 486

Number 4—(*continued*)

page

Elective Aortic and Mitral Valve Surgery in Patients Over 70 Years of Age
R. Canepa-Anson and R. W. Emanuel 493

Angiosarcoma of the Heart
Margaret Shackell, Anna Mitko, P. L. Williams, and G. C. Sutton 498

Case Reports 504, 508

Notices 512

Number 5

Rotational Excursion of Heart in Massive Pericardial Effusion Studied by Phased Array Echocardiography
H. Matsuo, M. Matsumoto, Y. Hamanaka, T. Ohara, S. Senda, M. Inoue, and H. Abe 513

Evaluation of Posterior Aortic Wall Echogram in Diagnosis of Mitral Valve Disease
R. J. C. Hall, S. E. Clarke, and D. Brown 522

Determination of Pressure Gradient in Mitral Stenosis with Doppler Echocardiography
Jarle Holen and Svein Simonsen 529

Echocardiography in Cardiovascular Drug Assessment M. A. Martin, and N. R. J. Fieller 536

Nomenclature and Classification of Congenital Heart Disease
M. J. Tynan, A. E. Becker, F. J. Macartney, M. Quero Jiménez, E. A. Shinebourne, and R. H. Anderson 544

Prevalence of Congenital Heart Disease in Black Schoolchildren in Soweto, Johannesburg
M. J. McLaren, A. S. Lachman, and J. B. Barlow 554

How to Determine Atrial Situs? Considerations Initiated by 3 Cases of Absent Spleen with a Discordant Anatomy Between Bronchi and Atria G. Caruso and A. E. Becker 559

Evaluation of Thallium-201 Exercise Scintigraphy in Coronary Heart Disease
R. G. Murray, J. H. McKillop, R. G. Bessent, J. G. Turner, A. R. Lorimer, I. Hutton, W. R. Greig, and T. D. V. Lawrie 568

Thallium-201 Scintigraphy in Diagnosis of Coronary Stenosis. Comparison with Electrocardiography and Coronary Arteriography
R. A. Corne, M. S. Gotsman, A. Weiss, D. Enlander, L. D. Samuels, Jean A. Salomon, B. Warshaw, and H. Atlan 575

Effects of Oxygen Administration, Bicarbonate Infusions, and Brief Hyperventilation on Patients with Pulmonary Vascular Obstructive Disease
Geoffrey Morrison and Fergus Macartney 584

Haemodynamic Studies in Veno-Occlusive Disease of the Liver
T. E. Kasturi, S. C. Manchanda, R. K. Tandon, M. Rajani, and M. L. Bhatia 594

Electrophysiological and Haemodynamic Basis for Application of New Pacemaker Technology in Sick Sinus Syndrome and Atrioventricular Block
Richard Sutton and Paul Citron 600

Cardiomyopathic Syndrome Caused By Coronary Artery Disease. III: Prospective Clinicopathological Study of its Prevalence Among Patients with Clinically Unexplained Chronic Heart Failure C. A. Boucher, J. T. Fallon, R. A. Johnson, and P. M. Yurchak 613

Case Reports 621, 624, 628

Correspondence 632

Notices 632

Number 6

Prognosis of Patients Paced for Chronic Atrioventricular Block
W. Ginks, A. Leatham, and H. Siddons 633

Complete Right Bundle-Branch Block. Echophonocardiographic Study of First Heart Sound and Right Ventricular Contraction Times
N. Brooks, G. Leech, and A. Leatham 637

Patients Treated in a Coronary Care Unit Without Acute Myocardial Infarction. Identification of High Risk Subgroup for Subsequent Myocardial Infarction and/or Cardiovascular Death R. Nordlander and O. Nyquist 647

Number 6—*(continued)*

page
REDUCTION OF EARLY VENTRICULAR ARRHYTHMIA BY ACEBUTOLOL IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION
Gail G. Ahumada, R. P. Karlsberg, A. S. Jaffe, H. D. Ambos, B. E. Sobel, and R. Roberts 654
RECOGNITION AND QUANTIFICATION OF MYOCARDIAL INJURY BY MEANS OF PLASMA ENZYME AND ISOENZYME ACTIVITIES AFTER CARDIAC SURGERY
A. van der Laarse, H. A. Davids, L. Hollaar, E. J. M. van der Valk, S. A. G. J. Witteveen, and W. Th. Hermens 660
ESTIMATION OF MYOCARDIAL INFARCT SIZE IN MAN USING 99^{m} TC POLYPHOSPHATE
G. J. Davies, B. Fakhrai, A. Morgan, and J. R. Muir 668
UHL'S ANOMALY R. J. Vecht, D. J. S. Carmichael, R. Gopal, and G. Philip 676
MAXIMAL SUPINE EXERCISE HAEMODYNAMICS AFTER OPEN HEART SURGERY FOR FALLOTS' TETRALOGY
Gordon R. Cumming 683
ANTIBODIES TO COXSACKIE B VIRUSES IN CONGESTIVE CARDIOMYOPATHY
G. Cambridge, C. G. C. MacArthur, A. P. Waterson, J. F. Goodwin, and C. M. Oakley 692
HEART SIZE AND FUNCTION IN ACROMEGALY H. M. Mather, M. J. Boyd, and J. S. Jenkins 697
LONG-TERM FOLLOW-UP IN PRIMARY PULMONARY HYPERTENSION
L. D. Suarez, E. E. Sciandro, J. J. Llera, and A. M. Perosio 702
CLINICAL ELECTROPHYSIOLOGICAL EFFECTS OF PROPRANOLOL ON NORMAL SINUS NODE FUNCTION
M. Vasquez, R. Chuquimia, N. Shantha, M. Khan, and O. S. Narula 709
COMPARABILITY AND REPRODUCIBILITY OF APEX CARDIOGRAM RECORDED WITH SIX DIFFERENT TRANSDUCER SYSTEMS J. L. H. Willems, B. Denef, H. Kesteloot, and H. De Geest 716
CASE REPORTS 727, 730, 734
OBITUARY: Arthur Morgan Jones 738
CORRESPONDENCE 740
INDEX 741

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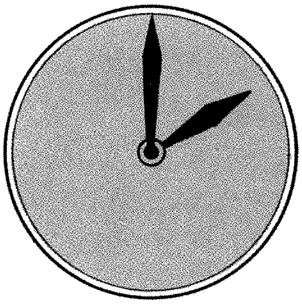

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CURRENT TOPICS:

Congenital Coronary Arteriovenous Fistula. Report of 13 Patients, Review of the Literature and Delineation of Management. Richard R. Liberthson, Karen Sagar, John P. Berkoben, Ronald M. Weintraub, and Frederick H. Levine 849

ORIGINAL ARTICLES:

Antiarrhythmic Drug Therapy in Survivors of Prehospital Cardiac Arrest: Comparison of Effects on Chronic Ventricular Arrhythmias and on Recurrent Cardiac Arrest. Robert J. Myerburg, Cesar Conde, David S. Sheps, Ruth A. Appel, Iris Kiem, Ruey J. Sung, and Agustin Castellanos 855

Editorial: Antiarrhythmic Therapy, Ventricular Premature Depolarizations and Sudden Cardiac Death: The Tip of the Iceberg. Leonard A. Cobb and Jeffrey A. Werner 864

Prevalence of Arrhythmias During 24-hour Electrocardiographic Monitoring and Exercise Testing in Patients with Obstructive and Nonobstructive Hypertrophic Cardiomyopathy (ASH). Daniel D. Savage, Stuart F. Seides, Barry J. Maron, Debra J. Myers, and Stephen E. Epstein 866

Effect of Verapamil in Infants with Paroxysmal Supraventricular Tachycardia. J. Soler-Soler, J. Sagristá-Sauleda, Alberto Cabrera, J. Sauleda-Parés, J. Iglesias-Berengué, G. Permanyer-Miralda, and J. Roca-Llop 876

The Cardiac Conduction System in Situs Ambiguus. David F. Dickinson, James L. Wilkinson, Kenneth R. Anderson, Audrey Smith, Sien Yen Ho, and Robert H. Anderson 879

Editorial: Positional Variations of the Heart and Its Component Chambers. Saroja Bharati and Maurice Lev 886

Echocardiographic Estimation of Ventricular Hypoplasia in Complete Atrioventricular Canal. Sudhir Mehta, Stephen Hirschfeld, Thimas Riggs, and Jerome Liebman 888

Anatomic Function in Women with Mitral Valve Prolapse Syndrome. F. Andrew Gaffney, Erling S. Karlsson, William Campbell, James E. Schutte, J. V. Nixon, James T. Willerson, and C. Gunnar Blomqvist, with the technical assistance of Willie E. Moore, Jr. 894

Mitral Valve Closure in Atrial Flutter. Mark A. Greenberg, L. Scott Herman, and Michael V. Cohen 902

Hemodynamic Factors Influencing Arteria lHypoxemia in Massive Pulmonary Embolism with Circulatory Failure. Francois Jardin, Francis Gurdjian, Pierre Desfonds, Jean-Luc Fouilladieu, and Andre Margairaz 909

The Pathophysiology and Diverse Etiology of Septal Perforator Compression. John B. Kostis, Abel E. Moreyra, Narayanan Natarajan, Maryhelen Hosler, Peter T. Kuo, and Hadley L. Conn, Jr. 913

Echocardiographic Evaluation of Ventricular Septal Aneurysms. A. Rebecca Snider, Norman H. Silverman, Nelson B. Schiller, and Thomas A. Ports 920

Effects of Nitroglycerin on Echocardiographic Measurements of Left Ventricular Wall Thickness and Regional Myocardial Performance During Acute Coronary Ischemia. R. Roger Komer, Amy Edalui, and William B. Hood, Jr. 926

Circadian Variation of Exercise Capacity in Patients with Prinzmetal's Variant Angina: Role of Exercise-Induced Coronary Arterial Spasm. Hirofumi Yasue, Shingo Omote, Akinori Takazawa, Masao Nagao, Kunihisa Miwa, and Satoru Tanaka 938

Coronary Arterial Spasm as a Cause of Exercise-Induced ST-Segment Elevation in Patients with Variant Angina. Giuseppe Specchia, Stefano de Servi, Colomba Falcone, Ezio Bramucci, Luigi Angoli, Antonio Mussini, G. Piero Marinoni, Carlo Montemartini, and Piero Bobba 948

Mechanism of Rest and Nocturnal Angina: Observations During Continuous Hemodynamic and Electrocardiographic Monitoring. Jaime Figueras, Bramah N. Singh, William Ganz, Yzhar Charuzi, and H. J. C. Swann 955

Uric Acid: A Risk Factor for Coronary Heart Disease? Victoria W. Persky, Alan R. Dyer, Elizabeth Idris-Soven, Jeremiah Stamler, Richard B. Shekelle, James A. Schoenberger, David M. Berkson, and Howard A. Lindberg 969

Comparison of Cardiovascular Responses to Static-Dynamic Effort and Dynamic Effort Alone in Patients with Chronic Ischemic Heart Disease. Robert DeBusk, William Pitts, William Haskell, and Nancy Houston 977

Impaired Maximal Rate of Left Ventricular Relaxation in Patients with Coronary Artery Disease and Left Ventricular Dysfunction. Silvio E. Papapietro, H. Cecil Coghlan, Dimitry Zissermann, Richard O. Russell, Jr., Charles E. Rackley, and William J. Rogers 984

Quantitative Left Ventricular Wall Motion Analysis: A Comparison of Area, Chord and Radial Methods. Harris J. Gelberg, Bruce H. Brundage, Stanton Glantz, and William W. Parmley 991

Regional Ejection Fraction: A Quantitive Radionuclide Index of Regional Left Ventircular Performance. Denis E. Maddox, Joshua Wynne, Roger Uren, J. Anthony Parker, John Idoine, Lawrence C. Siegel, Jane M. Neill, Peter F. Cohn, and B. Leonard Holman 1001

Usefulness and Limitations of Thallium-201 Myocardial Scintigraphy in Delineating Location and Size of Prior Myocardial Infarction. Gary S. Niess, Joseph R. Logic, Richard O. Russell, Jr., Charles E. Rackley, and William J. Rogers 1010

Effect of Left Ventricular Akinesis on Cardiac Performance, Experimental Study Using a New Model. Peter R. Maggs, Thomas P. E. Nener, and F. Henry Ellis, Jr. 1019

A Mathematical Model of the Dynamic Geometry of the Intact Left Ventricle and Its Application to Clinical Data. Jean G. Dumesnil, Rachad M. Shoucri, Jean-Louis Laurenceau, and Jules Turcot 1024

A Prospective Evaluation of His Bundle Block. John H. McAnulty, Edward Murphy, and Shahbudin H. Rahimtoola 1035

Intermittent Left Bundle Branch Block: Anatomic Substrate as Reflected in the Electrocardiogram During Normal Conduction. Richard Abben, Kenneth M. Rosen, and Pablo Denes 1040

The Role of Left Ventricular Conduction in the Electrogenesis of Left Ventricular Hypertophy An Electrophysiologic Study in Man. Eligio Piccolo, Antonio Raviele, Pietro Delise, Francesco Dainese, Pietro Pascotto, Giovanni Totaro, Frederico Sartori, and Daniele D'Este 1044

Treatment of Hypertension with Nifedipine, a Calcium Antagonistic Agent. Maria T. Olivari, Cesare Bartorelli, Alvise Polese, Cesare Fiorentini, Paolo Moruzzi, and Maurizio D. Guazzi 1056

Dopamine Beta-Hydroxylase and Plasma Renin Activity in Patients with Low-, Normal-, and High-Renin Essential Hypertension. William J. Lawton, Annette Fitz, Christine Grant, and David L. Witte 1063

CASE REPORT:

Right Atrial Myxoma: Unusual Clinical Presentation and Atypical Glandular Histology. Stephen Factor, William Frishman, Alphonzo Jordan, Charles Hellman, Uri Elkayam, Thierry LeJemtel, Joel Strom, Harold Unschuld, and Ronald Becker 1070

KEY REFERENCES:

Antiarrhythmic Drugs. Compiled by Benedict R. Lucchesi 1076

LETTERS TO THE EDITOR 1079

NEWS FROM THE AMERICAN HEART ASSOCIATION 1084A, Ad page

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